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P. J. DU TOIT,
Director of Veterinary Services and Animal Industry.

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THE INCIDENCE AND PATHOLOGY OF TUMOURS OF DOMESTICATED ANIMALS IN SOUTH AFRICA.

A Study of the Onderstepoort Collection of Neoplasms with Special Reference to their Histopathology

By

CECIL JACKSON, B.Sc., B.V.Sc.

FOREWORD.

The present number of the Onderstepoort Journal *differs from its predecessors inasmuch as it contains one article only. This departure from precedent was considered justified in view of the exceptional scope and importance of the subject dealt with in this work.*

Mr. Jackson imposed upon himself an arduous task. He undertook to study, classify, and describe the tumours in the extensive collection of pathological specimens at Onderstepoort. But he achieved more than that. He has presented a comprehensive, closely-reasoned, and critical study of neoplastic conditions in general in our domesticated animals.

It is considered that his striking contribution to our knowledge of new growths will prove to be of lasting value, not only to veterinary science, but also to human pathology. And so the hope may be expressed that this study may aid in the ultimate solution of that greatest unsolved problem in medicine, cancer.

P. J. du Toit,
Editor.

PREFACE.

SINCE the inception of a routine pathological diagnostic service at Onderstepoort over 18,000 pathological specimens have been submitted for histological diagnosis over a period of some fifteen years. Much of this material had been earmarked as of interest for further examination or for museum purposes and among it occurs a wealth of examples of neoplastic disease in the domesticated animals.

The present work is the result of a programme to make this material conveniently available for reference and further study, whereby it is proposed to establish a complete collection of microscopic preparations representative of the pathology of domesticated animals in this country serving at once as a check on the accuracy of the diagnosis of the macroscopic specimens in the extensive museum of pathology which has been built up at this Institute and supplementing the study of this material from the histological standpoint. In the preparation and arrangement of a microscopic collection of this type it is obvious that accuracy in diagnosis and uniformity of classification are the first essentials. In these two respects the compilation of that portion of the collection comprising the neoplastic diseases offered the most difficulty, and it was therefore decided to attack this part of the work first. With the completion of this chapter of the pathology there has been established an annotated and classified collection of histological preparations of the neoplasms which have been encountered among domestic animals in South Africa which not only has a statistical value(¹) but which gives instant access to preparations of the various kinds of tumours whose pathological-anatomical and histiological descriptions and whose position in the classificatory scheme are made available by the present work.

The collection is housed in steel cabinets (each of which is designed to accommodate 2,400 slides) containing slotted wooden trays in which the slides are vertically placed. A system of coloured cards is used to facilitate access to the different classes of tumours, and each slide is affixed to a cardboard label of the same size (with a window to admit light to the section) and on which (through the glass) may be read the species of animal, the site affected, the diagnosis and (where necessary) a summary of the histological features. At present approximately 3,000 slides of the neoplastic diseases are so stored, but it is intended that the collection should be a mobile one, allowing of constant expansion as more material is acquired and of revision and re-classification as our knowledge improves.

(¹) A small proportion of the earlier specimens have unfortunately been destroyed and a few have been used up in the preparation of sections for teaching purposes.

PREFACE.

Even in the course of its compilation, this collection proved of the greatest use in facilitating accurate diagnosis in difficult cases by providing a ready means of comparison. Reference to it shows also at a glance whether the tumour one is dealing with is a lesion rare or unknown in this country or elsewhere. The value which the collection has acquired at Onderstepoort has led me to feel that a presentation of its salient features would be of assistance to pathologists who have not access to these specimens and who may have to wrestle with the often exquisitely difficult problems encountered in the diagnosis of neoplasms. We all know how common it is in such cases to consult textbooks or other literature without obtaining the definite information we seek. It is in the hope that a more detailed study of the histological and especially the cytological aspects of oncology may prove of use in this connection that my comments on these aspects of the collection are here embodied as a text to which the systematic catalogue of the specimens provides an appendix (C). [Originally it was planned to incorporate in this appendix the descriptive protocols of all those tumours which had not been dealt with in the text. This project had to be abandoned on account of the length to which the latter grew.] The aim of this work has, however, in no sense been the providing of a textbook. Not only is the Onderstepoort collection, large as it is, deficient in certain kinds of tumours, but good general texts on neoplasms of animals already exist, both Feldman's (1932) textbook and Joest's *Spezielle Pathologie* providing a wealth of information regarding veterinary oncology and its bibliography. Rather has it been my aim to discuss those problems and describe those appearances which, for the very reason that they are so meagrely touched upon in the literature, caused me great difficulties when first I embarked on this work.

It is inevitable that in a task of this kind I have had to lean heavily on the co-operation and encouragement of many scientific friends. To Dr. P. J. du Toit, Director, and Dr. G. de Kock, Deputy Director of Veterinary Services, I am grateful for their approval and encouragement of this study. To my colleague Dr. A. D. Thomas I am deeply indebted. It is owing to his energy and enthusiasm for the study of tumours that a great many of the specimens have been obtained, and from his profound knowledge of microscopic pathology he has ever willingly advised me. I have also made use of the records left by present colleagues in and past members of the Department of Pathology. The surgical staff and poultry pathologists at this Institute have contributed many interesting specimens and much valuable information. To those who have been good enough to go out of their way to supply specimens which might otherwise never have received notice this Institute also owes a debt. Mr. R. Paine, M.R.C.V.S. (both as Government Veterinary Officer, Grahamstown, and as Officer in Charge, Allerton Laboratory) and Dr. G. Kind have been especially helpful in this respect, while many other veterinarians in Government Service, Municipal Service, and private practice have, in response to appeals, been very willing to collect specimens and to forward particulars thereof. Where possible acknowledgements of such co-operation are made in the text. I cannot sufficiently praise the excellence of the technical assistance which I have received from Miss Dorothy Armstrong, who has been responsible for the cutting and staining of the sections, among which many beautiful preparations are to be found. Mr. F. D. Horwell, who has been in charge of the records associated with the work, has prepared the two text figures. Mr. Th. Meyer has expended his usual care in the photography, which could not have been in better hands. I have also to thank several friends whose discussion of those problems in which our investigatory paths have crossed has been a constant source of inspiration to me, and would especially mention Dr. H. H. Curson, Professor of Anatomy, University of Pretoria, Dr. Joseph Gillman of the University of the Witwatersrand and Mr. A. P. Malan, Statistician at Onderstepoort. Lastly, I wish cordially to acknowledge the kindness of the State Librarian, Pretoria, and the Librarian of the National Central Library, London, through whose co-operation it was possible to borrow from British universities (Liverpool, Sheffield, and Aberdeen) copies of many important communications on tumours which are not available in our own libraries.

ONDERSTEPOORT, *November*, 1935. C. J.

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CHAPTER 1.

Introduction.

THE necessity of prefacing any study in comparative oncology with an apologia in which is pointed out the value of such investigation is, happily, becoming a thing of the past. In the purely morphological sphere, the investigations of pioneers such as Bashford and Murray, Cramer, and Joest have proved over and over again their worth, while from the biological aspect the epoch-making discoveries of Peyton Rous and of Fujinami in regard to transmissible tumours of domestic birds, and of Yamagiwa and Itchikawa in connection with the experimental causation of malignancy in mammals are nowadays familiar even to laymen. But much remains to be done. The pathology of tumours in animals is virtually a never-ending study to which everyone who encounters any considerable number of animals affected by neoplastic disease is bound to have something to contribute.

The Onderstepoort Collection of neoplasms of domesticated animals is one of the most complete in the world, and certainly the largest in any tropical or subtropical country. By its establishment is provided ready access to the direct study of the gross and microscopic pathology of almost every known kind of tumour of animals and of many little known or unrecognised ones. Anyone who cares to consult it will be rewarded by an advance in the knowledge, the foundations of which have been laid by those pathologists—Joest, Kitt, Joest and Ernesti, Sticker, Casper, and Feldman—whose general works on neoplasms of domestic mammals or birds have become classical, and by the many others who have contributed to the study of neoplasms of certain kinds or of certain organs.

The sources of the specimens have been: "district" specimens submitted by field veterinarians, private practitioners, and laymen for diagnosis, or submitted by abattoir officials as contributions to the museum; "local" specimens accruing from the routine autopsies both on hospital patients and experimental animals at Onderstepoort; while not a few tumour specimens have been obtained by colleagues in the Department of Pathology who have often gone out of their way to collect material. Many of the older specimens have suffered changes through long preservation, and in those cases where it was possible to gain assistance from the descriptions made at the time or from autopsy records such information has been made use of. In very many cases one could have wished for more complete information from the senders of specimens, especially regarding the site of occurrence, the presence of metastases, and the history of the subject. As a result of propaganda, the response of members of the profession to appeals for a fuller description of specimens has been very gratifying. It is beginning to be more widely recognised, not only that the accurate diagnosis of neoplasms does not depend entirely on microscopic examination of an often haphazardly selected fragment of the tissue, and that a full history of the subject and careful description of the fresh specimen *in situ* are of the greatest assistance to the pathologist; but also that the records at Onderstepoort are often invalidated by incomplete information. In a few instances in the past, even the species of the subject has not been stated, rendering such material almost worthless from the statistical point of view.

As might be expected, the intensive study of the neoplastic diseases at Onderstepoort has resulted in an apparent increase of their incidence. This serves to show of what limited value the actual figures are. These can be given only in terms of pathological specimens received, but they do at least serve to show how frequently the pathologist encounters tumours of domestic animals and what an important part these lesions play in routine diagnosis. Some 4 per cent. of all routine specimens are neoplastic diseases and in very many other cases a thorough knowledge of oncology is essential for correct interpretations; it is therefore obvious that any weakness in the diagnosis of such specimens must very seriously reflect on the efficiency of the routine diagnostic service. It has consequently been an important aim in this work to attempt to place on a surer and more uniform basis the diagnosis and nomenclature of animal tumours encountered in this country. To do this it is found necessary to pay close attention to the minute histological and more especially the cytological morphology of the tumours, with a view to making available more detailed descriptions than are usually to be found in the literature. I believe that more exhaustive descriptions in reports of tumours would lead to much greater clarity and would form a more satisfactory basis for comparison, apart from the value they have from the general biological standpoint. In the last analysis, however, the diagnosis of tumours still remains almost as much an " art " as a science, and no one can tell another how to diagnose neoplasms, but only how to learn to do so. Facility in diagnosis is to be obtained only by calling all available embryological and cytological knowledge to the assistance of one's mental equipment in pathology. It is this ramification of neoplastic pathology into several other spheres which renders it impossible to undertake its study without contributing in some measure to other phases of pathology and to our knowledge of normal morphology and of tissue and cell biology. As William James has said: " We learn most about a thing when we view it in its most exaggerated form "; and this generalisation is never more true than when applied to the observation of cells and tissues in their neoplastic manifestations.

PROBLEMS OF CLASSIFICATION.

The effective classification of neoplasms and closely related lesions presents one of the subtlest problems in pathology. Impatient as some people may be of the apparently barren nosological discussions in which our pathological literature abounds, nomenclature is yet the measure of the orderliness of the state to which a given biological subject has advanced. And one should distinguish between two dilemmas of nomenclature which may confront the pathologist, the one more elementary, the other more advanced: those difficulties of nomenclature which depend, not upon an insufficiency of factual knowledge, but rather upon the circumstance that thorough observation of the facts has brought us to a consideration of fundamentals, belong to the latter category; such classificatory discussions, undertaken when no longer doubt exists as to the actual nature of the facts observed, are to be respected as indicative of the depths to which observation has led the pathologist; not as confessions of ignorance but, on the other hand, as declarations of the interest which a challenging problem and an appreciation of its intricacies has aroused.

We are to-day committed to a classificatory system which rests upon a dual basis of histology and histogenesis (while in certain cases also aetiological criteria are used, e.g. especially in assessing transmissible tumours and tumour-like diseases). But our definitions of the cell types and of their histological products and the patterns in which these are arranged are often vague, as are also the criteria which are used as evidence of histogenesis. Regarding the latter, the difficult question of the significance of the phenomenon of tissue-continuity, so often tacitly assumed as a proof of histogenesis, will receive attention later in this work. It will be seen that, in some cases at least, one may fall into grave error through assuming that continuity of a neoplastic tissue with pre-existing tissue denotes an origin of the former from the latter, because pictures of most intimate continuity may arise between a neoplastic tissue and the structures that it is invading. Yet one would not, on the basis of this observation in the case of certain tumours, wish entirely to sweep away the phenomenon of continuity as evidence of histogenesis in other cases, where indeed we often have little else to depend upon in our determination of the origin of a tumour. Judgment must be used in each individual case, and I have not hesitated in allowing myself to be influenced by the appearance of continuity as evidence of histogenesis in many cases. While admitting that we are often working with poor or double-edged tools in carving out our classification, we must nevertheless strive to make them render the most effective and safest service possible.

There is always the tendency for the enthusiastic histopathologist to multiply nomenclatural terms on the basis of variation in those morphological appearances which characterise the histological varieties of tumours or which provide evidence of histogenesis; and this tendency has to be kept in check for two reasons: firstly, apparently genuine morphological distinctions, not corresponding with clinical, prognostic, or aetological differences, may be of little interest to any one except the histopathologists themselves; secondly, non-essential morphological variations may be mistaken for essential ones and may then be erroneously assessed as being of sufficient importance to warrant the establishment of distinct classificatory varieties. In a sense, almost every tumour has its pathological-anatomical individuality, and we should bear in mind that although " no two leaves are alike ", yet " there is nothing new under the sun ". Enthusiasm for morphology, if carried to its extremes, could doubtless succeed in devising a new name for almost every tumour encountered. The morphological variations that have been mentioned as non-essential from the classificatory standpoint include two main types:—(1) Further stages of development which are undergone by the tumour tissue: the difficulty here arises that we usually examine a tumour at a single stage of its development, and try to understand what is temporally a continuous process by means of studying a single " cross-section in time ". The danger may be illustrated by the simile of cutting up a cinematograph film into its constituent units, and arranging them as a gallery of differently labelled photographs: one and the same entity may be classified by different names if isolated in different stages of its unfolding. This may especially be the case in neoplastic and pre-neoplastic processes occurring in organs whose cells are characterised by a certain vigour of proliferative ability and a variable growth-mode, such as the liver and the thyroid. In the former, for example, it is probable that a proliferative process may be variously classed as nodular hyperplasia, adenoma, or carcinoma depending on what stage it has reached when the specimen is examined. While we cannot, as histopathologists, do away with these distinctions, it should be remembered that they are, to some extent at least, artificial: and the occurrence of intermediate grades between these three types of proliferation warns us against considering these classificatory compartments watertight in all cases. Similar considerations apply in connection with certain " metaplastic " transformations of tumour tissues which are nothing but reflections of the potentialities of their normal homotypes: it is, for example, a very normal process for bone to replace cartilage, so that in many cases we should hesitate to make any radical distinction between chondrogenic sarcoma (chondro-sarcoma) and osteochondrogenic sarcoma (osteochondrosarcoma). On the other hand, such objections need not apply to the distinction between, for example, lymphocytoma and myelocytoma or erythroleucosis: although the cells of the one may represent the reflection of a normal differentiation-potentiality of the other, the whole nature or pathology of the processes may be very different. (2) Secondary changes occurring in neoplasms may sometimes be difficult to distinguish from primary or essential characters: thus we attempt to distinguish between a fibroma affected by oedematous or mucoid changes and myxoma; between " perithelioma " and tumours in which necrosis, affecting all the cells except those in the neighbourhood of blood-vessels, has produced a false peritheliomatous appearance. In such cases we may have to be guided less by the grosser histological features than by a detailed study of the cell types. Similarly, changes occurring in the stroma of tumours (e.g. osteoplasia) are to be distinguished from an essential osteogenetic tendency of the tumour cells. Such examples could easily be multiplied and are quite familiar to pathologists.

It thus becomes abundantly clear that enthusiasm for detailed morphological analysis as a basis for nomenclature must be kept on a tight rein. Pathological nomenclature has a natural history of its own: firstly, a stage of childhood, where merely on account of ignorance one term may serve to cover what are in reality a number of distinct processes; secondly, an age of adolescence, where names must perforce be multiplied in order to pigeon-hole the various appearances for future comparison and revision until, with time, greater experience shall have been gained; and finally, the stage of maturity, when comparison has succeeded in determining what are but natural developmental changes, in weeding out the secondary from the essential morphological distinctions, and in correlating morphological appearances with clinical and above all with aetiological considerations; with a resulting re-simplification of the terminology. Nomenclature is thus, far from static or permanent, nothing more than a summary of the knowledge at any given moment. It starts by being indiscriminatingly simple and ends by being discriminatingly simple. The stage of adolescent nomenclature has always to face discouragement and scientific ridicule by those who are over-anxious for progress or by those who do not appreciate the natural growth of classification. But multiplication of terms during that stage is unavoidable and is, indeed, essential to progress. The re-simplification of nomenclature may, it is true, sometimes be overdue, pathologists not seldom being reluctant to " put away childish things ". We see to-day, for example, a movement to abolish the term " hypernephroma " and to bring the adrenal tumours back into line with previously established types (adenoma, carcinoma, neuroblastoma). The same applies to " thymoma "; while some more ruthless (but equally logical) reformists are urging more radical changes in nomenclature because they consider that the older terms have lost their significance in the light of newer aetiological knowledge or of more fundamental embryological considerations. Oertel (1931) contends that the time-honoured distinction of carcinoma from sarcoma has to-day lost its significance. But the majority of pathologists hesitate to agree that the time is ripe for radical reform, although all look forward to the day when, on the secure foundation of aetiological enlightenment, we shall be able to put away the classification which has served us so long but so indifferently well. The experimental production of mesoblastic tumours (sarcoma, myelocytoma) by the agent (tar) which is already well known as a cause of epithelioma may well be the writing on the wall foreshadowing the advent of such reforms: from the experimental standpoint it would seem that all are " cancers ", whether of epithelium, connective tissue, or haemopoietic tissue. Yet one must be cautious not to confuse a cause with a disease: to the clinician actinomycosis of a lymph-node remains a lymphadenitis and actinomycosis of the lung a pneumonia, although the aetological identity is established; and the clinician will, however the pathologist may classify, rightly continue to concern himself primarily with the disease and secondarily with causes of disease.

It is intended in this work to follow the general outline of accepted histological-histogenetic classification of neoplasms, so far as possible and in accordance with the need of presenting intelligibly the material contained in the Onderstepoort collection, although the sub-classification of the main groups will be discussed in detail when dealing with the tumours in question. The arrangement of the tumours in chapters has no special classificatory significance, but is made mainly for convenience of presentation.

PROBLEMS OF DIAGNOSIS.

The completion of this work necessitated a re-examination of many cases that had already been examined in the routine. A small percentage of such cases had been erroneously assessed, in relatively few cases no diagnosis at all had been ventured, and in a large number of cases revisions of the nomenclature employed had to be undertaken in order to conform to a uniform system. Most of the more recent specimens in the collection were submitted to me directly, and the research investigation was then combined with the examination for purposes of routine diagnosis. In this work, it was inevitable that some insight was obtained into the difficulties which have beset my colleagues and predecessors at this Institute regarding the diagnosis of neoplasms. It is impossible to mention all of these, but some of the most important and the most fruitful sources of error appeared to be as follow:—

Differentiation of Neoplastic from the Non-neoplastic Lesions.

This, as is well known, often involves extremely puzzling problems. Especially are here concerned those hyperplastic processes which approach neoplastic grade, of which common examples are:—

(1) *Fibroblastic proliferations of the skin of equines.*—It was found that many lesions of the skin of equines which had been variously diagnosed as sarcomas or granulomas were in reality the "sarcoids" described later in this work. There was, on close histological analysis, seen to exist no uniformity in the assessment of such lesions, and even tumours which I considered as sarcomas had been diagnosed as (cellular) fibromas. There appears to be little doubt, however, leaving aside the more obvious errors arising from insufficiently close study of such lesions, that grades of proliferation actually intermediate between sarcoma and granuloma exist. To these the term "sarcoid" has been applied. One can easily pick out from the collection a closely graded series of specimens showing every transition in histological structure from granuloma to "spindle-celled" sarcoma. Differential diagnosis depends, as pointed out in Chapter VII, on the demonstration of anaplastic changes in the proliferating fibroblasts, especially nuclear irregularities and a distinct increase of the nucleolar-nuclear ratio.

(2) *Hyperplastic processes of liver and thyroid epithelium.*—These are dealt with in Chapter IV. It is difficult in the case of liver-cell tumours to distinguish between adenoma and carcinoma. The occurrence of intergrades has resulted in the introduction into the literature of the non-committal term "hepatoma". It is also possible to observe transitions from nodular hyperplasias to benign tumours and judgment depends on an assessment of the degree of independence and autonomous growth (*aus sich heraus*) which the tissue has attained, especially as shown by encapsulation, by pressure against the surrounding normal tissue, and by the attainment or possibility of attainment of considerable dimensions by the proliferating area. The same applies to the distinction between nodular hyperplasia and thyroid adenoma. Here, also one feels that one may be dealing with a biologically continuous process, and that our classificatory distinctions are to some extent artificial.

(3) Many *nodules composed of adrenal cortical tissue* and diagnosed as adenomas prove to be nothing but accessory cortical nodules composed of normal adrenal cells which have during embryonic development come to occupy an abnormal position and arrangement with reference to the rest of the gland.

(4) *Cystic conditions* may be mistaken for tumours. Among such were cystic degeneration of the pituitary (mistaken for adenoma), congenital bile-duct cysts (erroneously diagnosed as bile-duct-cell adenoma of the liver), cystic Brunner's glands in the sheep (diagnosed as adenoma of the duodenum), and cystic lymphangiectasia of the serous membranes of birds (likely to be confused with lymphangioma).

(5) *In fowls*, many lesions had been diagnosed as neoplasms, and called endotheliomas, peritheliomas, round-celled sarcomas, which on critical re-examination proved to be nothing but granulomas in which proliferating capillaries or round cell infiltration and multiplication were prominent. The subcutis of the bird appears to have remarkable powers of proliferation in response to various stimuli and its haemopoietic potentialities are well known to avian haematologists. One should in any case be cautious before diagnosing endothelioma of fowls. I have never encountered such a tumour nor apparently have Feldman (1932) or Joest and Ernesti (1916) in the examination of their extensive collections; and although both Begg (1927) and Furth (1934) have reported transmissible " endothelioma " of fowls, the justification of the term from the histological and histogenetic standpoints cannot be regarded as satisfactory. In granulation tissue of the bird, the proliferating endothelium may be very prominent, actually dominating the picture. The differentiation of granulomas characterised by prominent proliferation of lymphoid elements from lymphocytomas also requires caution and one should be at pains, by examining a number of sections, to exclude an inflammatory origin for the lesion, especially by the employment of bacterial stains. Chronic inflammatory lesions of the abdominal serosae of fowls, which arise especially from the irritation caused by free egg-yolk in the peritoneal cavity are not infrequently mistaken for implantation-carcinosis or sarcomatosis. The nodules on the serosae are usually rather uniformly small in size, and their diagnosis depends on the finding of infiltrating and proliferating macrophages, especially associated with deposits of yolk. The distinction from implantations of histocytic sarcoma, in which lipophagocytosis is often also a prominent feature, depends finally on the demonstration of the presence or absence of anaplastic changes in the cells and of invasive growth. The lesions under discussion often occur together with implantation-metastases, for the reason that the primary tumour responsible for the latter is in most cases situated in the ovary, invasion of which organ favours the setting free of egg-yolk in the peritoneum; and it must consequently be remembered that not all of the miliary nodules found on the serosae in cases of abdominal malignancy of fowls need necessarily be young secondary neoplasms. In fowls difficulties may also arise in the distinction between leucotic diseases and lymphatic proliferative processes: hyperplasia of lymphoid cells in the liver is sometimes difficult to distinguish from lymphoid leucosis: the distinction is to be based on the degree of differentiation which the cells tend to undergo, the extent of the process (difficulty of lesions of lymphoid leucosis in the earliest stages!), and the presence or absence of actual invasive growth; the latter feature is most important, and in all cases diagnosed as lymphoid leucosis, one should be able to demonstrate actual aggresive growth, e.g. in the hepatic parenchyma. Similarly, myeloid cells often appear to participate in inflammatory hyperplasias in fowls

and in addition to granulocytes which have infiltrated the damaged tissues from the bloodstream one may encounter local proliferation and differentiation of granular cells from their precursors. Such lesions may often be seen in the ovary, whose stroma appears to have wide potentialities of proliferative response in infections or irritation caused by ruptured ova. Such lesions have to be distinguished from myelocytoma (often also found in the ovary) or myeloid leucosis. Again, judgment depends largely on the demonstration of a cause for inflammation or on the finding of actual invasive growth. It may be said that such problems encountered in avian pathology are especially likely to embarrass those whose experience is largely confined to mammalian pathology. The same fundamental criteria apply, but a slightly different set of values is necessary in assessing many of these proliferative processes in birds, some of whose tissues appear to possess a readier and more elastic responsiveness to stimuli than is the case in mammals.

Difficulties in the Assessment of Malignancy.

The establishing of the nature of the tissue and the cells involved in a neoplastic proliferative process having been accomplished, difficulty often occurs in deciding whether one is dealing with a benign or a malignant tumour. Further, the interpretation of malignancy, of (e.g.) carcinoma as opposed to adenoma, varies somewhat. In this work we have based our conception of malignancy on the criterion of invasive growth, whether or not actual metastases are or even are likely to be established. As is well known, however, the decision may present extreme difficulties and in some cases it may be necessary to rely largely on features of the cytology, especially the demonstration of anaplastic changes in the cells. Yet even anaplastic changes may be absent in tumours capable of invasive growth. The difficulties of the differential diagnosis of adenoma and carcinoma of the liver have been referred to and will be returned to in detail in Chapter IV. They may be very embarrassing, if not impossible of solution, in cases where one is required to make a diagnosis from a small fragment of the tumour, especially if it does not include the boundary between the neoplastic and the normal tissue. There were also encountered lesions diagnosed as fibroma, of which, had sufficient attention been paid to anaplastic cellular changes, especially nuclear abnormalities and nucleolar enlargement, the sarcomatous nature would have been apparent. Many lesions in fowls, especially of the ovary, commonly referred to as adenomata, are really carcinomas. The tumours may lack anaplastic cellular changes, have a slow growth rate, and fail to produce true metastases(¹), but their ability to penetrate the serosa under which they develop and to give rise to transcoelomic implantations stamps them as malignant tumours which should therefore be termed carcinomas. In this connection it may here be pointed out that in this work the term malignant adenoma has not been admitted; the tumours described as such are carcinomas, the criteria of a

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(¹) This is no unusual character of avian carcinomas, which having no or little tendency to invade blood-vessels fail to produce metastases readily because the anatomy of the bird does not favour lymphogenous metastasis. Allowance should be made for this in assessing the nature of epithelial neoplasms in avians.

carcinoma being its epithelial nature and its capacity for invasive growth; in the last analysis, its actual structure does not count, the invasive capacity overriding all other criteria, however useful these may often be in the study of a tumour.

Other Difficulties.

Some thymomas had been diagnosed as lymphosarcomas, the situation of the tumour not having been taken into account and detailed histological study having been lacking. A small thyroid adenoma had been diagnosed as spindle-celled sarcoma because a superficial resemblance of the spindle-shaped cells to fibroblasts had been considered, rather than the determination of whether these cells actually were fibroblasts: the criterion of the latter is of course their fibroplastic capacity. In human pathology the striking way in which proliferating cells arising from thyroid epithelium may resemble fibroblasts is well known, and the actual existence of sarcoma of the thyroid is still a vexed question. The diagnosis of embryonal nephroma, both in fowls and domestic mammals was often found to give rise to difficulty. The "sarcomatous" moiety of these tumours may often be overlooked, the neoplastic spindle cells being mistaken for a cellular stroma. Indeed, it is not certain whether lesions which still are classified in the collection as simple adenoma or carcinoma of the kidney are not also embryonal tumours, in origin identical with the embryonal nephromas, the only difference being that in the simple tumours full realisation of the epithelioid potentialities of the cells has been attained. In such cases, however, one has no means of proof; but it is interesting in this connection to recall the theory that most, if not all adenomata, are to be ascribed to anomalies in embryonic development.

As is mentioned in more detail under the headings of basal-cell epithelioma and of the contagious (venereal) tumours of the dog, the basal-cell tumours were often mistaken for adenomata. Usually the tissue from which they were supposed to arise was not stated, but in some cases a sweat gland origin, or in others (these lesions occur on the head) an origin from a salivary gland was thought of. The transmissible canine tumours, on the other hand, were sometimes mistaken for basal-cell tumours. There is of course little similarity, but in both cases a histogenesis cannot be determined.

Less serious differences of opinion which arose on re-examination of the material after routine diagnosis concerned embryonal tumours of the mammary gland of bitches, which had often been diagnosed as simple carcinoma or simple (spindle-celled) sarcoma due to failure to take account of any but the predominating type of proliferation or failure to cut a sufficient number of sections from different parts. Confusion had also arisen in the distinction between liver-cell and bile-duct tumours of the liver and also of primary from secondary liver tumours: in many of these cases an opinion (which is essential to a complete diagnosis) had not been ventured.(²)

(²) It must not be thought that the foregoing remarks are intended as any reflection on the excellent pathological routine service carried out by my colleagues at Onderstepoort. From them the author has received every possible help in the correction of mistakes and he himself is one of the routine workers who in the past has been guilty of many errors in tumour diagnosis.

Enough examples have been given to show that the accurate histological diagnosis of neoplasms of animals (like those of man) often presents great difficulties. The remedy appears to lie largely in acquiring that experience which is gained by familiarity not only with all kinds of true neoplastic processes, but also with processes resembling or likely to be confused with the neoplastic. In this country, such experience is readily to be obtained by consulting the annotated histological collection of neoplasms at Onderstepoort.

THE NUCLEOLUS IN TUMOUR CELLS.

Scarcely any attention has been paid to the morphology of the nucleolus in neoplasms of domesticated animals. Occasionally one finds it mentioned in descriptions of tumours that the nucleolus is "easily visible" or "not easily distinguished", or that it is "prominent". Such terms do not convey with accuracy the actual state of the nucleolus. Regarding human tumours, in Ewing's *Neoplastic Diseases* we read that "in epitheliomas great excess and multiplicity of paranuclein bodies is somewhat characteristic, while in endotheliomas the nucleoli are relatively small". This statement leaves one with but a vague impression of the state of the nucleolus in tumours of man: whether it is intended to apply to all of the several kinds of epitheliomas, whether the feature is confined to epitheliomas, whether in endotheliomas the relative smallness ot the nucleoli is judged by comparison with the large nucleoli of epitheliomas or by comparison with the non-neoplastic endothelial cell, and what the position is in the cells of the other kinds of tumours is left doubtful. Further, we have no information regarding nucleolar changes other than those which concern number and size.

More recently MacCarty (1928) and MacCarty and Hammeder (1934) have investigated the question of the size of nucleoli in human tumour cells with more precision, and have concluded that an enlargement of the nucleoli is constant in all malignant tumours, while in benign tumours and non-neoplastic proliferations such enlargement does not occur. The absolute size of the nucleolus is not measured, but the size is stated in terms of the "nucleolar-nuclear ratio", by which is meant the areal ratio existing between a nucleus in section and its nucleolus. They do not make distinctions between the various classes of malignant tumours, concluding with the general statement that the average nucleolar-nuclear ratio(³) is 1:5 to 1:17 for malignant cells and 1:13 to 1:45 for non-malignant cells. I believe that these authors have performed a valuable service by drawing attention to the prevalence of nucleolar enlargement in malignant tumours; but in making the generalisation just mentioned, they omit to define what they mean by a malignant cell or a malignant tumour, conceptions which are by no means free from ambiguity. Further, it appears to me that in considering nucleolar enlargement in any tumour cell, it is essential to take into account the size of the nucleolus of the corresponding normal cell: for it is obvious that any given n:N ratio may represent very different degrees of nuceolar enlargement in different kinds of cells: in normal body cells, great variations in the n:N ratio occur, and it is well known

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(³) Subsequently in this work this term is abbreviated to n:N.

that in some (e.g. nerve cells, cells of the adrenal cortex, epithelial cells in general) the ratio is large or considerable, while in others (e.g. fibrocytes and endothelial cells) it is small, and in still others (e.g. leucocytes) nucleoli are not ordinarily visible at all. Thus a n : N ratio of, say 1 : 10 may reflect little enlargement of the nucleolus of some epithelial cells, while it may represent considerable enlargement of the nucleolus of e.g. an endothelial cell. A diagram of the range of n:N ratios which will be referred to in this work is shown in fig. 1.

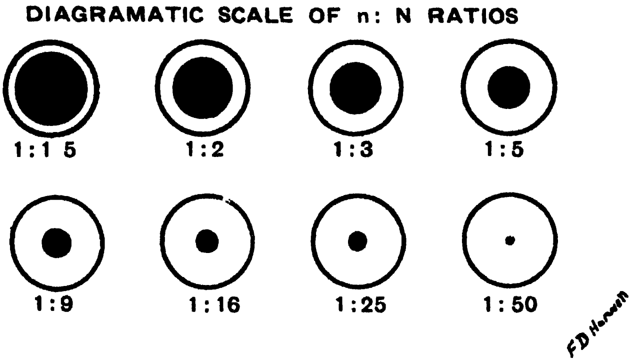

FIG. 1. Diagram of the various nucleolar-nuclear ratios referred to in the text.

Of changes in shape and texture and staining reaction of the nucleolus I find no mention in veterinary pathology and have been unable to find clear statements in human pathology. Pianese (*cit.* Ewing) as early as 1896 described certain bodies within the nucleus, occurring especially in the tumours of the liver, as " pseudo-adipose and cystic degeneration of nucleus ". It seems almost certain that he was actually dealing with altered nucleoli, and similar bodies which I had the opportunity of observing in human liver tumours(4) are undoubtedly of nucleolar origin and similar to those which we shall describe in animal tumours. It would appear probable, however, that the latter provide more suitable material for study, in that the changes in question are more often encountered, especially in the extreme form which Pianese described as a hyalinosis of part or the whole of the nucleoplasm.

1. *Changes in size.* - In tumours of domestic animals, increase of the n:N ratio (see e.g. figs. 2, 3, 4) is very often found in malignant tumours, and never in benign tumours, in my experience. By malignant tumours I here mean those that are characterised by invasive growth and in which, therefore, metastasis occurs or a possibility of metastasis exists, and I include here the tumours sometimes spoken of as malignant adenomas, e.g. of the liver. The largest n:N ratios are to be found in acanthoma, in hepatoma, in the transmissible (venereal) tumours of the dog and those heart-base tumours (Chapter XI) which have a similar morphology to them, and in sarcomas. Increase of n:N ratio may also be encountered in other malignant tumours e.g. endothelioma, mesothelioma. It was not

(4) Examined through the courtesy of Dr. J. Gillman and Dr. C. Berman.

encountered in thymomas. Although the thymomas are not usually associated with metastasis, they grow invasively and must be reckoned as malignant tumours; and in some endotheliomas it was also absent. Members of both these groups of tumours would appear to constitute exceptions to the rule of MacCarty and Hammeder that an increased n:N ratio is absolutely constant in malignant tumours. The largest n:N ratio mentioned by these authors was 1:5. In the tumours of domesticated animals, ratios of 1:2 have not infrequently been encountered. The largest ratio I have observed, viz. 1 : 1·5 was encountered in a cell of a "mixed-celled" sarcoma of the fowl (5128).

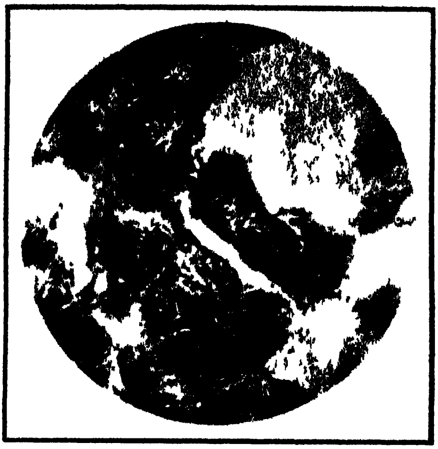

FIG. 2.—A distorted and enlarged nucleolus in "mixed-celled" sarcoma of the fowl (8487; 750 ×)

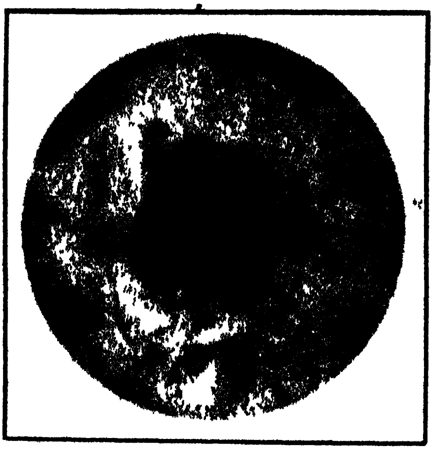

FIG. 3.—An enlarged, twisted, and elongated nucleolus in a neoplastic macrophage occurring in mixed-celled sarcoma of the fowl (8487; 750 ×).

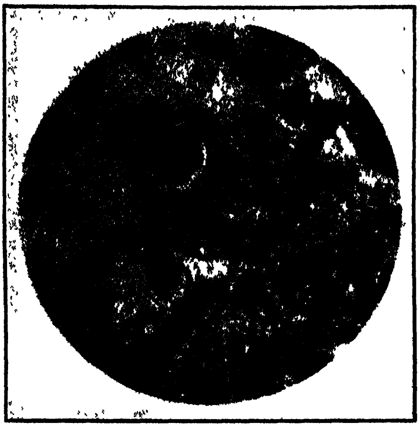

FIG. 4.—A greatly enlarged and angular nucleolus in "mixed-celled" sarcoma of the fowl (14117; 950 ×).

2. *Changes in Shape.*—In many different kinds of malignant tumours a departure of the nucleoli from the spherical shape is to be seen. The most common change is to an oval or rod shape. Nucleoli may also assume angular, lobed, pyriform, or twisted forms. These changes may be seen especially in the mixed-celled sarcomata of fowls (Figs. 2, 3 and 4) in which the elongated nucleolus may also lie with its length at right angles to the long axis of the nucleus, but also in a variety of mammalian malignant tumours.

3. *Gross Changes in Appearance.*—A very characteristic appearance, which is apparently identical with that described by Pianese in human tumours, may be seen in certain tumours of mammals and of birds, especially in malignant tumours. I have encountered it in liver-cell carcinoma of the sheep and fowl, cholangiocellular carcinoma, neurfibroma, and thymoma of the ox, carcinoma of the lung and heart-base tumours of the dog, cortical hypernephroma of the sheep, "sarcoids" of equines, and "mixed-celled" sarcoma of the fowl. When reaching its full development (Figs. 8 and 9) this phenomenon consists in the presence within the nucleus of one or more large, glassy, scarcely-staining or faintly eosinophilic, rounded or irregularly rounded bodies, which may almost completely occupy the nucleoplasm. As seen in this form, these bodies would probably be referred to as intranuclear inclusions, and it does not seem unlikely that some of the bodies which have been described as such may be of a similar nature. These hyaline bodies in the nuclei of tumours are, however, altered nucleoli. All stages in their formation from nucleoli (Figs. 5, 6 and 7) can be observed: the process starts as a vacuolation of the nucleolus, a single rarefied, lighter staining area appears in the centre (Fig. 6), or there may be multiple vacuoles (Fig. 5) which as they enlarge confer upon the nucleolus the multilocular or morulate appearance of a Negri-body. Such vacuoles increase in size, or fuse, until almost the whole nucleus may be distended by a

Figs. 5, 6, and 7.—Stages in the development of hyalinisation of the nucleoli of neoplastic cells of animals :—

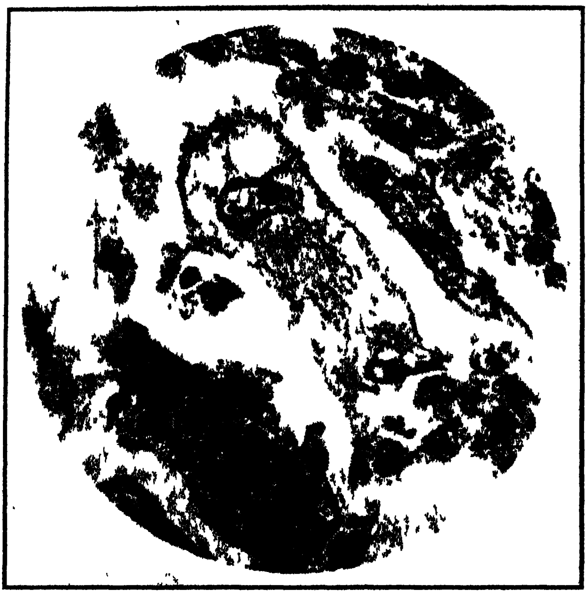

Fig. 5.—Minute vacuolations appearing in a nucleolus of a cell of histiocytic sarcoma of the fowl. Note also the nucleolar enlargement in two of the cells. (8487 ; 750 ×).

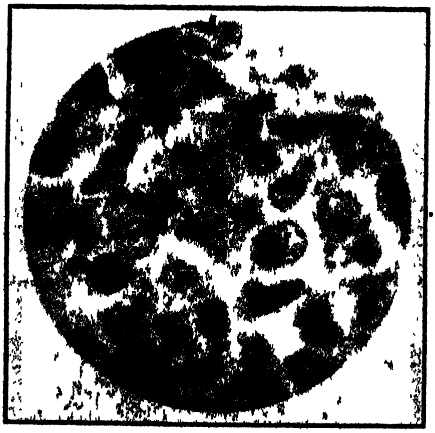

Fig. 6.—More advanced stage of vacuolation in a nucleolus of a cell in a heart-base tumour of the dog : A considerable area of the nucleolus is occupied by a central vacuole. (15848 ; 750 ×).

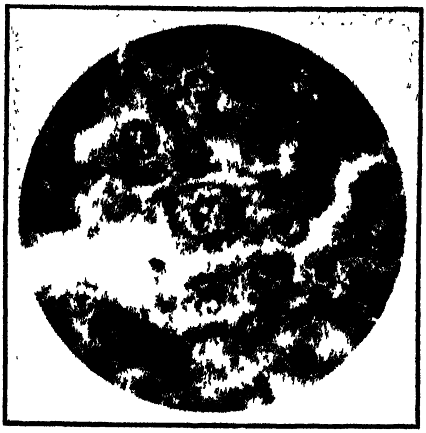

Fig. 7.- Almost the whole of one of two nucleoli in a cell of a heart-base tumour of the dog is occupied by a hyaline vacuole. (15848 : 750 ×).

single " inclusion " which is now quite unrecognisable as a nucleolus (Fig. 9). If the nucleus be originally multinucleolate, one or more of the nucleoli may suffer this change, so that either there may exist multiple " inclusions " within a nucleus (Fig. 10) or inclusions and nucleoli may co-exist in the nuclei (Fig. 7). In the latter event, especially, it is likely that a nucleolar origin of the inclusion body might be hastily dismissed by the observer: Cowdry and Scott (1931), for example, mention the demonstration of a normal nucleolus within the (liver-cell) nucleus as evidence for the non-nucleolar origin of certain intranuclear inclusions observed by them in the (non-neoplastic) liver cells of dogs. I am not concerned here with the accuracy of their conclusions regarding the genesis of the bodies in question, nor do I wish to question such conclusions, which were not based on this evidence alone; but merely to point out that, since multiple nucleoli are a common feature of nuclei, the observation of an unaltered nucleus in a cell is no evidence that an inclusion body within the same nucleus may not represent an altered nucleolus. It would seem necessary, however, in view of the proof which is advanced in this work of the nucleolar origin of intranuclear " inclusions " in tumours, critically to re-examine the possibility that some of the other intranuclear inclusions may not have a similar origin. Further, it would seem necessary, in considering the n : N ratio, to include such hyalinised nucleoli in the determinations.

It seems profitless to discuss the biological significance of nucleolar changes in pathological conditions until we are more certain of the function of the nucleolus under normal conditions. Recent work, e.g. Gardiner (1935), goes to show that this function is a somewhat " humbler " one than was in earlier times suspected or than is suggested by the appellation of the term " germinal spot " to the nucleolus of the ovum, and that the nucleolus may represent nothing more than a store of metabolites or food material and is chemically quite different from chromatin. It is as yet not clear why some cells should have multiple or prominent nucleoli, others inconspicuous ones, and still others apparently none at all.

FIGS. 8, 9, and 10.—Culmination of the nucleolar hyalinisation process illustrated by figs. 5, 6, and 7 in fully developed intranuclear " inclusions " in the tumour cells of animals :—

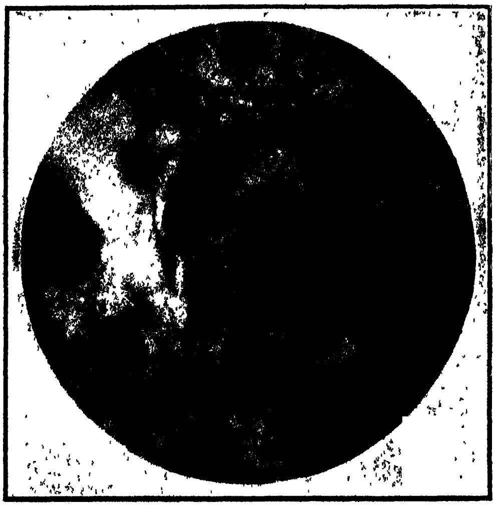

Fig. 8.—Two cells of a bovine cholangiocellular carcinoma affected by " inclusions." (6278 ; 1150 ×).

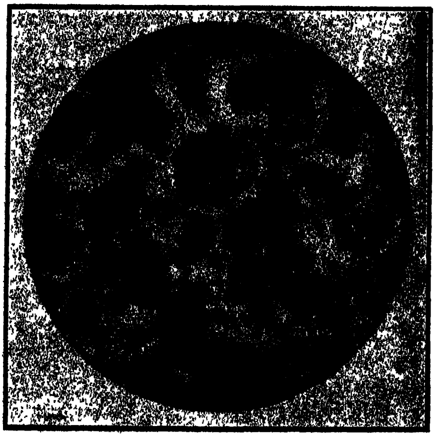

Fig. 9.—Large " inclusion " occupying the greater part of the nucleus of a cell in the pulmonary metastasis of a heart-base tumour of the dog (same case as figs. 6 and 7). (15848 ; 750 ×).

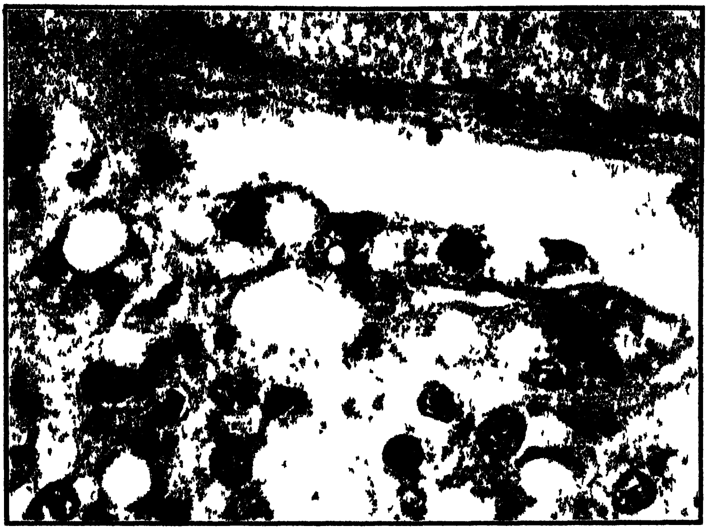

Fig 10. Multiple "inclusions" in a single nucleus of an hepatocellular carcinoma of the sheep: three are clearly visible and a fourth (to the right) is slightly out of focus. (13320; 750 ×).

The Stroma and Intercellular Matrices of Tumours.

The stroma (proper) of a tumour results from a progressive response of elements of mesenchymal derivation to the presence of the tumour cells, whereby the latter receive support and nourishment and are able to maintain an arrangement in a more or less characteristic pattern. Such stroma consists, therefore, typically of collagenous connective tissue and vessels, which are present in varying amounts. It may also in certain cases consist of other tissues, e.g. smooth muscle, bone, etc. From this stroma it is necessary to distinguish (*a*) pre-existing blood-vessels and connective tissue belonging to the organ in which the tumour is developing or which it is invading; such tissue may fulfil all the functions of a newly formed stroma, in which case it is convenient to refer to it as a stroma; (*b*) a tissue resulting from an actual neoplastic transformation of the stroma: it is here not always easy to decide what are the limits to which a stroma may overgrow before one is warranted in considering it a separate neoplastic entity. This is especially the case when, as mentioned above, other tissues than fibrous tissue and vessels enter into its formation. This question is discussed under the subject of the mixed tumours; (*c*) a neoplastic moiety imitating the normal derivatives mesenchyme, such as may result (in embryonal tumours) from a multipotentiality of the tumour cells themselves: thus, as will be described when dealing with the mixed neoplasms, in embryonal nephromas, for example, fibre-producing spindle-shaped elements which are a part of the neoplastic proliferation itself must not be mistaken for a highly cellular stroma; (*d*) intercellular matrices or neoplastic blood-vessels which result from the differentiation of the tumour cells themselves: it is the identification and assessment of such structures that play so important a part in the accurate diagnosis of simple tumours of mesenchymal origin, which are, indeed, classified on the basis of this differentiation (fibroma, chondroma, fibroplastic sarcoma, angioplastic endothelioma, etc.). The necessity of employing, even in routine diagnosis, staining methods designed to differentiate specifically these different products of tumour cells is often insufficiently appreciated. Failure to investigate these aspects of the morphology of tumours results only too often in erroneous or inaccurate diagnoses, in insufficiently detailed descriptions in the literature, and not seldom in a complete impasse in the attempted identification and classification of a tumour. This is especially the case in regard to that intercellular matrix known as (fibrillar) reticulum, whose proper demonstration is often the first essential in the accurate study of certain sarcomas, endotheliomas, and mixed tumours, and their differentation from carcinomas, etc. It is well known of course that carcinomas, in contradistinction to sarcomas, lack such intercellular matrices, in virtue of their epithelial nature. But the position with regard to tumours of endothelial cells, some of the tumours (erroneously) called " round-celled sarcomas ", thymomas, and certain mixed or embryonal tumours is often left very obscure. In revising the routine diagnoses of tumours of animals in this country I found this to be one of the most prolific sources of error, both in actual diagnosis and in the descriptions which were recorded. Thus in solid endotheliomas, tracts where the tumour cells themselves produced abundant intercellular fibrils, thus assuming the nature of fibroblasts, were erroneously taken for the stroma (Figs. 146 and 147); and in mixed embryonal tumours, such as those of the dog's mammary gland and the embryonal nephromas of various species, the mistaking of fibril-producing neoplastic cells for a true stroma led often to an inaccurate diagnosis of a simple tumour, e.g. carcinoma. All these difficulties in diagnosis will be dealt with in detail in their proper places, and are mentioned here in explanation of the prominence which the study of the phenomena described often receives in the microscopic protocols in this work.

Two further phenomena, which are of more general biological significance, concern firstly the evidence which will be presented regarding the mode whereby fibres are produced by cells: it will be recalled that considerable differences of opinion have arisen concerning the extracellular *versus* the intracellular production of connective-tissue fibrils. In some of the tumours studied in this work it has been possible to show very clearly that collagen may arise within the cytoplasm of cells, as is believed by some authors to be the universal mode of formation of connective-tissue fibrils (e.g. Lewis, 1917, Mall, 1901-2, *et al.*). Other workers (e.g. Maximow, 1928, Dolijanski and Roulet, 1933), consider that fibrils are first deposited between the cells, under the influence of the latter but not by a direct conversion of their cytoplasm, while still others have advanced the surprising view that collagen may be deposited at sites remote from fibroblasts by a direct transformation of fibrin (Baitsell, 1916). The attitude of Wolbach (1933) to some extent reconciles these opposing views: in brief his conclusion is that the precursor of collagen, although intercellular in position, consists in a liquid cytoplasmic product excreted by the cells. It is not possible here to enter more fully into this controversy; but the observations which will be made in connection with the histiocytic ("mixed-celled") sarcomas and the embryonal nephromas of birds serve to show that intracytoplasmic deposition is at least one of the ways in which collagen may be developed (Figs. 11 and also 117). This observation need by no means necessarily be regarded as conflicting with Wolbach's views on the mechanism of fibril-production in the case of *non-neoplastic* fibroblasts; for the intracytoplasmic deposition of collagen in *neoplastic* cells might find its explanation in a failure of the timeous excretion from the cells of the liquid collagen-precursor formed in the cytoplasm. Collagen resulting from an excessive transformation of the cytoplasm of the cells of avian histiocytic sarcomas may appear as a complete capsule for each element when the cells are more widely separated; or when the cells are more closely placed they may be welded into a single mass consisting of alternate layers of cytoplasm and collagen-transformed cytoplasm (Fig. 117). In embryonal nephromas of birds, a very abortive attempt to form collagenous matrix may be observed when the collagen developing locally within the cytoplasm does not separate itself therefrom, resulting in actual nodal inclusions of this substance within the cytoplasm (Fig. 11).

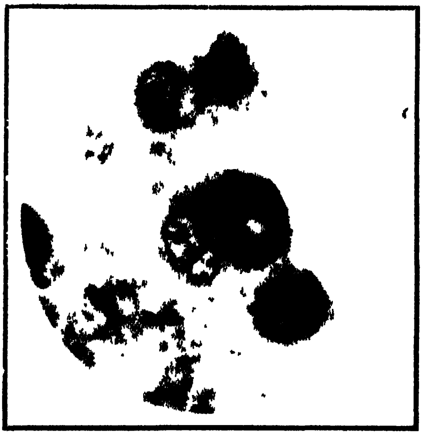

FIG. 11.—Intracytoplasmic deposition of a globular mass of collagen in a cell of the embryonal nephroma of the fowl (16143; 1150 ×). Van Gieson stain.

Secondly, in this work mention will often be made of the association of reticulum fibrils with neoplastic endothelial cells. A view which has in recent years gained much ground is that from the general vascular endothelium is to be distinguished a system of reticulo-endothelial cells which are distinguished by their phagocytic powers, by their association with reticulum fibrils, and possibly by their participation in haemopoiesis. This view has much to recommend it, and from certain standpoints (the mechanisms of defence, of the segregation of foreign and endogenous particulate matter, and of haemopoiesis) it is perhaps an essential conception and one which has been most productive of knowledge. Yet the exclusive participation of these cells in the production of reticulum is open to much doubt: Allen (1927) has presented evidence that in the endothelium of the renal glomeruli may be found reticulum fibrils, and in this work, as will be seen later, it was often observed that neoplastic endothelial cells of angiogenous origin may not only be associated with a rich production of reticulum fibrils (Fig. 147) but may actually differentiate into cells indistinguishable from fibroblasts and concerned in the formation of collagen (Fig. 146). This is not surprising in view of the demonstration by Maximow (1925) that, in tissue culture, endothelium gives rise to typical fibroblasts. But much confusion has resulted from a failure to recognise this transformation in endotheliomas: as has been mentioned above, the transformed portions of such tumours are usually mistaken for a true stroma.

The study of the metamorphoses which cells are capable of undergoing and of the formed products which they are capable of manufacturing in their normal environment is supplemented to great advantage by the observation of these potentialities in cells when growing in abnormal environment: in tissue culture and in neoplasms.

THE ATTEMPTED ESTIMATION OF THE GROWTH-RATE OF TUMOURS FROM EXAMINATION OF FIXED SPECIMENS.

It has been attempted to determine the growth-rate of tumours by ascertaining the proportion of cells in mitotic division at a given moment (i.e. at the moment of fixation or death of the tissue). This proportion of dividing cells per thousand cells is known as the mitotic index (Willis, 1932). Assuming that this determination is made under ideal conditions (viz. that the count is absolutely representative of the tumour as a whole—to ensure which great labour and examination of many sections from different parts of the specimen may obviously be necessary), the index may yet fail accurately to reflect the growth-rate of the tumour, for two reasons:—Firstly, the method assumes that the division-time (i.e. the period taken for the mitotic process to be completed) is constant in different cells and in different tumours; yet we have little information regarding the division-time of the cells of higher animals and, so far as I can see, no justification for assuming that it is constant, especially for different kinds of cells. A tumour which has a mitotic index of 2 may thus actually be growing at the same rate as one whose mitotic index is 1 per thousand, if the cells of the first tumour take twice as long to divide as those of the second tumour. Willis compared the growth-rate of tumours with that of their own (hepatic) metastases, so that he was dealing not only with the same kind of cells but with cells of identical ancestry: there is, therefore, in such a case, more justification for assuming a more-or-less constant average division-time, although the assumption is not beyond dispute. Where, however, one attempts to compare different tumours, and especially different kinds of tumours, great caution should be exercised in identifying the mitotic index with the growth-rate. Secondly, it is generally believed that amitotic division plays a part in the multiplication of cells, especially in certain kinds of tumours. In some sarcomata, for example, it is believed by many authorities that amitosis may actually predominate over mitosis. For this reason it is doubtful whether, strictly, one is even justified in assuming that the mitotic index is a true reflection of the number of cell divisions in a given volume of the tissue. This factor is doubtless of minor importance, but when one is dealing with certain tumours it is at least worth bearing in mind.

With all its drawbacks, however, the mitotic index remains the only method whereby one can express with more precision statements such as " mitotic figures are frequent, or present, or occur here and there ". One frequently hears it said that benign tumours of a certain kind of tissue are to be distinguished from their malignant counterparts by the presence of mitotic figures, or by the frequency of mitotic figures. But often it is found that between the benign tumours and malignant tumours the difference in mitotic indices (like the differences in so many other " diagnostic " features) proves to be one of degree and that a graded series of mitotic frequency occurs. Were these ideas expressed precisely, one would at least have something to attack in argument. Sometimes the erroneous statement is made that the presence of mitoses is a peculiarity of malignant as opposed to benign tumours. But it is to be noted that in some malignant tumours mitoses may be very hard to find and an index of less than 1 is common. On the other hand, in many benign tumours mitoses can be found, providing that one has the patience to search long enough. Considerable counts may be obtained in rapidly growing infectious benign tumours such as the contagious buccal papillomatosis of dogs. The truly neoplastic nature of this disease is of course open to doubt. The following table gives an idea of the frequency of mitotic figures in some of the common tumours:—

TABLE OF MITOTIC INDICES OF SOME COMMONER TUMOURS.

Species.	Tumour.	Mitotic Index.			Number of Cases on which Average is Calculated.
		Lowest.	Highest.	Average.	
Various......	Acanthoma.............	2	13	5	39
Canine......	Basal cell epithelioma....	< 1	4	1·8+	6
Bovine......	Carcinoma hepatocellulare	0	2	0·6	5
Ovine.......	Carcinoma hepatocellulare	—	4	2·6	3
Bovine......	Adenoma hepatocellulare.	—	—	0	1
Porcine......	Adenoma hepatocellulare.	—	4	—	—
Bovine......	Carcinoma cholangiocellulare............... ..	2	3	2·7	3
Canine......	Carcinoma cholangiocellulare.................	—	—	4·5	1
Various (mammals).	Fibroplastic sarcoma.....	< 1	4	1·7+	15
Various (mammals).	Angiogenous endothelioma	< 1	3	—	—
Ruminants...	Thymoma..............	0	< 1*	0+	6
Bovine......	Mesothelioma...........	2	3	2·5	4
Canine......	Contagious (venereal) tumour...............	3	15	6·6	11
Canine......	Contagious buccal papilloma................	—	6	—	—
Fowl........	" Mixed-celled " sarcoma.	< 1	5	1·6+	7
Fowl........	Embryonal nephroma....	< 1	3	1·2+	5
Fowl... ...	Ovarian carcinoma.... .	< 1	2	1·7	5

NOTES.—In cases where an index of less than 1 (< 1) is recorded, at least 2,000 cells were counted without observing a mitotic figure; the figure is thus actually below 0·5, and for purposes of averaging has been counted as nil. The average figure is thus an unknown fraction higher than the figure given, as denoted by the + sign.

Where a count of nil (0) is recorded, mitoses were not demonstrable after exhaustive searching.

* See page 214.

Some features of interest appearing from the foregoing table are:—The absolute (15) as well as the average (6·5) highest index was found in the contagious venereal tumour of dogs. Second in both these respects stand the acanthomas (11 and 5 respectively). Basal-cell epithelioma (in man a slowly-growing tumour) may have an unexpectedly high count (e.g. 4, in one case). Invasive liver-cell tumours (carcinoma hepatocellulare) of oxen cannot be rigidly distinguished from non-invasive tumours (adenoma hepatocellulare) on the basis of the mitotic index: in the former the index may be 0 in some cases, although usually it is higher; in the only case we have of the latter an index of 0 was recorded, while in the pig a count of 4 was obtained for a liver-cell adenoma. In the sheep, carcinoma hepatocellulare had a higher index than in the ox and no case was encountered in which mitoses were absent. Carcinoma cholangiocellulare has a higher average index than carcinoma hepatocellulare. Considering the average figures, one may be surprised that the highest indices do not reach such high figures as might be anticipated.

TECHNIQUE EMPLOYED.

I have left a description of the technique employed until after the discussion of the n:N ratio and of the mitotic index, for both these have to be mentioned again here.

Fixation and Staining.

Most specimens, as was inevitable, had been fixed in formalin, and had to be mordanted in Zenker's prior to the application of fibrillar stains. This process proved very successful, although less clear and brilliant pictures are obtained than with initial bichromate fixation. But in the case of the majority of the later tumours which I examined, fixation in Helly's fluid (Zenker's 9, neutralised formaldehyde 1) was ensured by sending supplies (of the unmixed constituents) to those likely to encounter tumours. The fixation of thin pieces (4-6 hours) is left in the hands of the sender, who subsequently washes the material overnight under a running tap and forwards the specimens in 60 per cent. alcohol, in which they may lie indefinitely without deterioration. Along with these Zenker-formol(5) fixed fragments, senders of tumours were requested to send the remainder of the tumour preserved in 10 per cent. formalin.

As a general routine both frozen and embedded sections of each tumour were used and in all important cases a number of pieces were selected from representative parts of the specimen. The stains employed were haemaluin-eosin, van Gieson, and Sudan III in every case, while in nearly all cases Mallory's triple stain was also employed for the study of reticulum. In a great number of cases Mallory's phosphotungstic acid haemotoxylin and May-Grunewald-Giemsa staining were used, for fibrils and for bacteria and haematological cytology respectively. In selected cases Bielchowsky impregnation was carried out. Peter's and Heidenhain's modifications of Mallory's acid-fuchsin-analine-blue-orange-G method were tried but found for my purpose to give no advantage over the ordinary " triple stain ".

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(5) This is undoubtedly the best general fixative for histological investigation of tumours of animals, provided that formalin-fixed pieces for fat-staining also submitted.

Where tumours were obtained fresh, air-dried, May-Grunewald-Giemsa stained smears were prepared if feasible. By this means not only was cytological study of some of the tumours facilitated, but in some cases a rapid diagnosis could be based on such smears: I found that the following diagnoses could be confirmed with reasonable or complete certainty from smears, especially if the surgeon had previously consulted the pathologist and had exhibited the case, so that one knew the various possibilities that were to be suspected: acanthoma, basal-cell epithelioma, endothelioma, fibroplastic sarcoma (distinction from equine " sarcoid " very difficult), endothelioma, contagious venereal tumour of dogs, lymphocytoma(6) of fowls. Further, by such means actinomycotic and other granulomata can usually readily be eliminated. Where tumour diagnosis depends largely on topographical relationships of the tissues or on the demonstration of intercellular matrices, obviously smear diagnosis must not be attempted. I had only once the opportunity to attempt diagnosis of a liver tumour (fresh material encountered at meat inspection) from a smear: in this case the neoplastic cells were easily recognisable as of the liver cell type, and because they happened to show great anaplasia, a diagnosis of primary liver-cell carcinoma was made. Doubtless, however, in the case of the less anaplastic liver-cell tumours, where difficulty arises in the distinction of carcinoma from adenoma, smear diagnosis might be most unreliable.

Measurement of the Nucleolar-nuclear ratio.

A technique for this determination has been published by MacCarty and Hammeder (1934), depending on projecting by means of a camera lucida the images of the nuclei with their nucleoli and tracing the outlines with a planimeter. A similar method was tried, obtaining great enlargement with a Zeiss projection microscope, and tracing the outlines on paper. Two methods of arriving at the relative areas of the nuclear and nucleolar tracings were tried: the first by tracing on to finely-ruled graph-paper and counting the included squares; the second by measuring the circumferences of the tracings by means of a sensitive planimeter. Accurate results are obtainable, but the method is too laborious for the examination of many hundreds of specimens. The same applies to a method that was tried whereby the tracings were obtained on graph paper by means of an Abbe drawing apparatus. It was felt that great accuracy was not a requisite, and the method by which most of the figures were obtained was by means of a " dot-and-circle graticule "(7). This consists of a circle of glass, which like any ocular micrometer, is introduced into the eyepiece of the microscope. On it are etched a graded series of circles of more or less standard size and a series of dots corresponding in size (Fig. 12). Calibration of the absolute areas with various lens systems is performed by means of measuring the diameters against the scale of a stage micrometer. The relative areas of the circles (and dots), reckoning the smallest as 1, is then determined. The scale of areas which is in use at this Laboratory is graded from 1 to 900. To determine the n:N ratio, the nucleus and the nucleolus of a given cell are matched with the circles or dots respectively (it being usually more convenient to match the nucleus with a circle and the darker staining, opaque nucleolus with a dot).

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(6) Recently the value of the smear method for rapid diagnosis of neurolymphomatosis gallinarum (in which the same cytological picture is seen as in lymphocytoma) has been pointed out by Downham and Crompton (1934).

(7) I have to express my thanks to Dr. A. J. Orenstein, C.M.G., and to Mr. H. S. Patterson, for drawing my attention to the existence of such graticules and for suggesting that I might find one of use. The graticule was supplied by Messrs. Rheinberg & Co., Ltd., London.

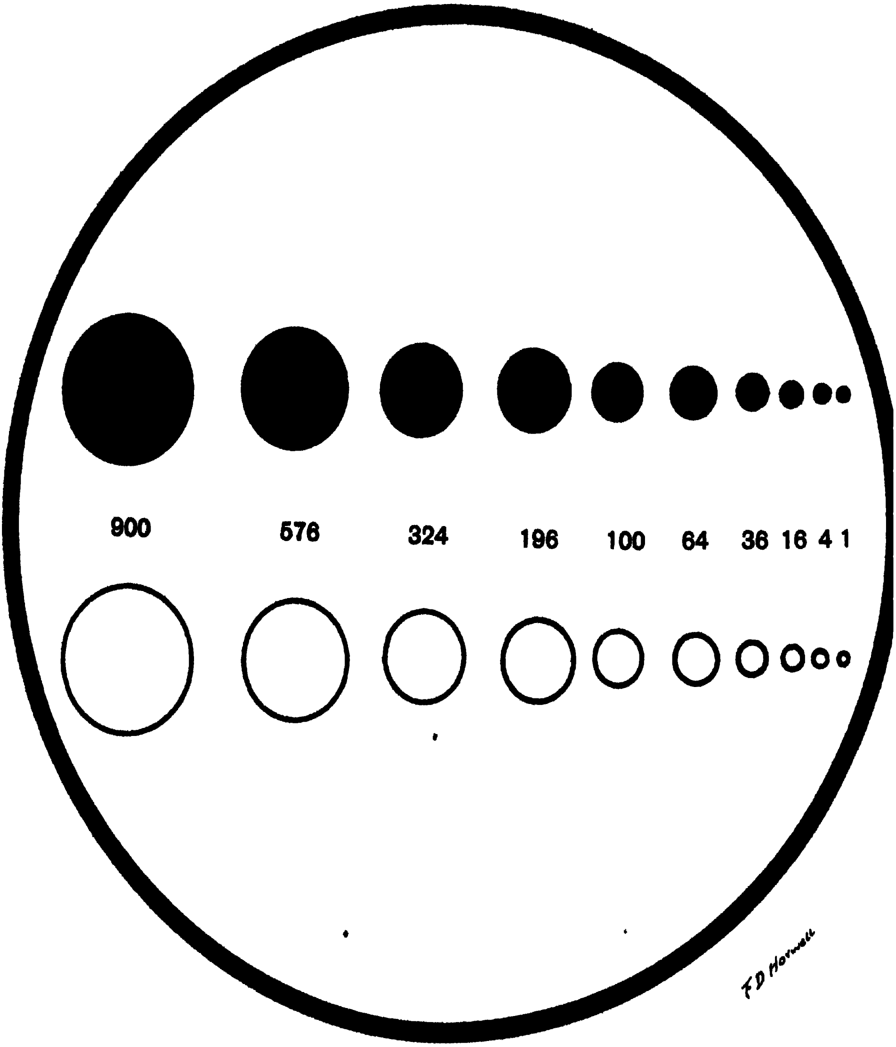

FIG. 12.—Dot-and-circle ocular micrometer use for estimation of n : N ratios; the numbers indicate the areal relationships.

The matching may be done by actual superimposition of the dot or circle on the object, but it is found that with very little practice one becomes just as accurate at matching when the object and the scale lie alongside or near each other. As has been said the method as I have used it is rather rough, there being only 10 standard areal sizes between 1 and 900 on the scale. If greater accuracy were desired, more closely calibrated scales might doubtless be constructed. A further objection is that not all nucleoli and nuclei are circular in section. However, fairly accurate matching of irregular shapes against the circles may be done by experience. In cases of gross irregularities and where it is desired to measure a particular nucleus affected by such, one of the other methods mentioned, or even direct measurements with an ocular micrometer may be resorted to. The n:N ratio of MacCarty and Hammeder is calculated for many cells and an average taken. This procedure is very laborious as a routine, and was only carried out in special cases. More usually a few cells considered average in respect of n:N ratio were selected by visual inspection, and their ratios measured. What interested me more was the determination of the maximal ratios encountered, for if, as MacCarty and Hammeder contend, one can speak of a " malignant cell " and such malignancy is indicated by an increase of n:N ratio beyond certain limits, then surely even a single enlarged nucleolus encountered in a tumour denotes malignancy, inasmuch as a tumour which has even one " malignant " cell is malignant or destined to malignant growth. But it is of course, as is well known, not advisable to speak of a " malignant " cell in the morphological sense, there being no single constant morphological accompaniment of malignancy (see Borst, 1933). Nevertheless, it is true that in benign and non-neoplastic cells the nucleoli usually remain within strict limits of size, and in most benign tumours not a single n:N ratio can be found which falls definitely on the wrong side of the borderline(⁸), if hyalinised nucleoli be disregarded.

Mitotic Counts.

The technique of mitotic counts has been described by Willis (1932) and is simple, although very laborious. In this work the labour of counting a thousand cells was usually shortened by calculating the mean number of cells enclosed within a given field and then simply noting the number of fields searched. Further reduction of labour may be achieved by introducing into the ocular a smaller square or circle ruled on a glass screen, estimating the average number of cells enclosed thereby, and then determining the proportion of the whole field which it encloses. In making mitotic counts, it will be found that great variation is obtained in different parts of the same tumour. Willis therefore made several counts in different parts. In the present work, this was not done, save in special cases. It is felt that in practice, one wishes to know " the worst " of any tumour, and what is of chief interest therefore is an indication of the growth-rate(⁹) in the most rapidly growing parts, not in parts which are necrobiotic, ill-nourished, or what-not. As a general rule, therefore, the count was made in what, after a preliminary inspection,

(⁸) As exceptions may be mentioned bovine neurofibroma, porcine; see hepatocellular adenoma and some tumours diagnosed as lymphangioma in this work.

(⁹) However inaccurate this may be. See the remarks made previously.

was considered to be the most rapidly growing or flourishing part. Further, in most cases, only a thousand cells were counted and the number found in mitosis was given as the index. If mitoses were present, but not found in counting a thousand cells, the index was given as less than 1 (<1). If mitoses could not be found, the index was recorded as nil. In all cases, apart from the actual count, the tissues were widely scrutinised to determine the presence or absence of mitoses and an index of nil was not recorded unless exhaustive search had failed to disclose a dividing cell.

CHAPTER II.

Tumours of Epithelium.

The Problem of Classification.

THE customary attempt to separate, as a group, tumours of epithelium at once meets with difficulties which do not always seem fully to have been appreciated. In the first place there is the almost insuperable drawback of the lack of any generally accepted and satisfactory definition of epithelium—satisfying, that is, to the oncologist as well as to the histologist and the embryologist. To the histologist epithelium " consist of cells of various shapes which are usually connected with one another without an appreciable amount of intercellular substance " and " arranged in sheets or layers of different thicknesses which either cover an even surface, or are rolled into tubes, or invaginated into small sacs " (Maximow, 1930); or (it should be added) form " solid cellular cords, more or less regularly arranged,which have no relation to a free surface " (Elwyn and Strong, 1932). Such definitions might well be held to include under the term epithelium both the endothelial lining of the vascular system and the (mesothelial) lining of the coelom, as well as certain elements of the nervous system not usually recognised as epithelium; while the position with regard to the thymic reticulum cells (see "thymoma") and the elements of the adrenal medulla (see " tumours of the adrenal ") is made far from clear. Embryological considerations give us but little assistance, since not only is epithelium as defined above derived from any one of the three primary germ layers; but from ectoderm and entoderm (as well as from mesoderm) arise cells which have exclusively or largely a supporting function (neuroglia cells, thymic reticulum cells) and which do not possess the characteristic of being arranged in close contiguity to one another. For such reasons there has never been a satisfactory definition of carcinoma—a category which is vaguely conceived as comprising malignant tumours the " type cell " of which is epithelial. But it is not clear whether this expression implies merely a morphological resemblance of the neoplastic cells to the epithelial prototype, or actually a derivation therefrom. These questions are indeed left unanswered, the classification of tumours and perhaps especially those of epithelium remains unsatisfactory and the scope of the terms undefined. The nomenclature has served well in the childhood of the science of oncology and although we have outgrown it we are left with nothing to put in its place. It is customary, however, to exclude from the tumours of epithelium those composed of the elements of the nervous system and of endothelium, while to-day most authorities are agreed that it is desirable to place under separate categories those arising from the thymic parenchyma and from the cells of the coelomic lining. There is also much to be said for the practice of including as epithelial tumours some which, however lacking (as regards morphology and arrangement) their cells may be in similarity to epithelium, have been proved or are believed to have arisen from epithelial cells. This practice cannot, however, be carried to its logical conclusions which would mean that all tumours must be considered as of epithelial derivation, since at one stage in embryonic development, as is well known, all the cells are arranged as epithelia, the modifications whereby arise the mesenchymal derivatives and the nervous derivatives, etc. being secondary.

Under this general category we have to consider tumours both of squamous and of other (e.g. glandular) epithelia. Here also no sharp division exists. It is customary to consider malignant tumours of the squamous type of epithelium (whether or not the latter undergoes differentiation) as a subgroup, epitheliomata, and under the same heading have often been placed certain benign or not clearly malignant neoplasms which arise from the accessory epidermal structures (of ectodermal origin). Great confusion surrounds the proper placing in the classificatory scheme of certain tumours of ectodermal origin. These are: malignant tumours arising from accessory epidermal structures such as sweat glands and sebaceous glands, which are usually simply termed carcinoma; further epithelial tumours of the breast should logically be considered as being among the epitheliomas, but this is not done(¹). It is apparent that in the present state of confusion any grouping must be highly arbitrary; and it is not our task in this work to set up a new classification, but merely to fit our own material into the scheme as intelligibly as possible.

The epithelial tumours in the Onderstepoort collection fall under the following heads: *cornu cutaneum*, epithelioma (including acanthoma, basal-cell epithelioma, and epitheliomas of the sebaceous gland type), adenoma, and carcinoma. There are further certain tumours with epithelial characteristics (possible neuroblastomas and epitheliomatoid melanomas) which are discussed in separate chapters. From the scope of epithelioma are excluded tumours of the mammary parenchyma and from the scope of carcinoma tumours of mixed character of the mammary gland of the dog and of the kidney of fowls and mammals (embryonal nephroma). These will be discussed under the mixed tumours. Papillomata also are dealt with under the mixed tumours (in Chapter X), for reasons which will there appear.

1. Cornu cutaneum.

Examples of this neoplasm were found only in ruminants. Among four bovine cases the skin of the dorsal region of the head (frontal or nasal regions) was thrice affected. One of these cases has been described by Brown (1935a). In the fourth case the skin of the tail was affected; the growth did not form a typical horn but a globular mass of keratin which may perhaps be rather of the nature of a hyperkeratosis. In the fifth case (Fig. 13) the external ear of a sheep (ovine 6142) was affected by a horny tumour of very regular form similar to that described by Beatti (1916).

(¹) It must be remembered that in the French pathology there is a tendency to call all carcinomas epitheliomas. This classification does not apply here.

Among these cases is not included a specimen of a horny outgrowth in the nasal region of a bovine (12902) which was developed in response to those traumatic and irritative influences to which calves are sometimes subjected by the natives of Barotseland and which have been described by Purchase (1935) It is uncertain whether this growth (hyperkeratosis?), which has been illustrated by Martinaglia (1933), is to be regarded as neoplastic and equivalent to the "spontaneous" cutaneous horns.

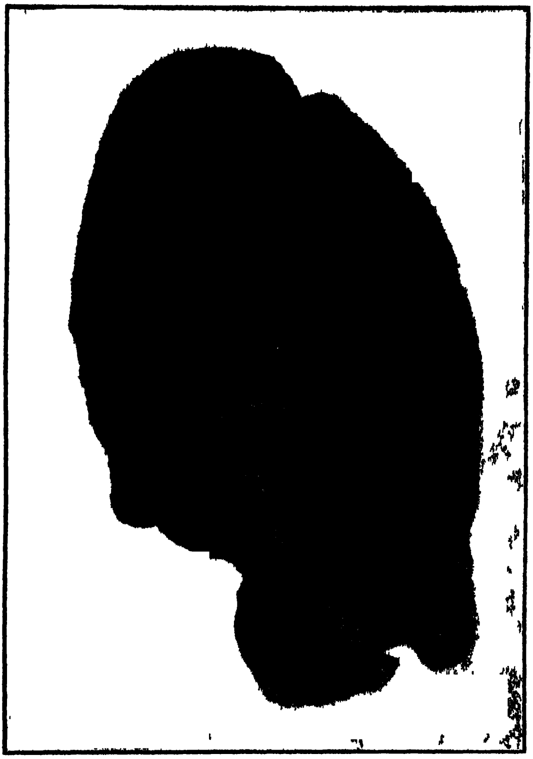

FIG. 13.—*Cornu cutaneum* of the external ear of a sheep (6142; nat. size.)

2. **Epithelioma.**

(Tumours derived from squamous epithelium or its derivatives, excluding the mammary gland.)

(*a*) ACANTHOMA.

Malignant tumours characterised by prickle cells and often also by "pearls" or concentric keratinizations are by far the most frequent malignant tumours of domestic mammals, the Onderstepoort collection containing 94 tumours of this type. Acanthomas are the most common tumours of oxen in this country; in the Angora goat they are equally as frequent as melanotic epitheliomas; in equines they are exceeded in frequency only by "sarcoids"; in the dog, only by the contagious venereal tumours; and in the sheep, only by (gland-cell) carcinomas. They are among the rarer neoplasms of the fowl and have not been encountered in the cat or in the pig. Their site of occurence varies greatly in the different species:—In both horses and oxen they are most commonly found affecting the orbital region, and when the specimen is obtained at an early stage, an origin from the conjunctival epithelium can be determined. In the sheep they have been observed with equal frequency in the orbital region and on the " scalp " (fronto-parietal region). In the Angora goat, as has been shown by Thomas (1929), the site of predilection is the perineum. In the dog they are widely distributed, but are not seen in the orbital region or elsewhere on the skin of the head. In the fowl, the leg below the tarsus was most often affected. Other common sites for these tumours are the penis or prepuce of the horse and the dog, the rumen of the ox(²) and the buccal mucosa of the dog. An unrecorded location for this neoplasm in the sheep is the omasum (one case). This tumour (Fig. 14) was situated at the omaso-abomasal orifice and produced hepatic metastases (Fig. 15).

Regarding the acanthomas of the dog, the prepuce or abdominal skin was the site of predilection. Less otten the buccal mucosa (gums and hard palate respectively) was affected.

The acanthomas of the fowl affected the skin of the leg (tarsal or metatarsal region) in two cases and the neck in one case.

It is interesting to note that roughly 97 per cent. of acanthomas in domestic animals in this country are of ectodermal origin (e.g. skin, conjunctiva, buccal mucosa) and approximately only 3 per cent. of entodermal origin (fore-stomachs). Also that in spite of the frequency of the tumour in the goat, constituting 29 per cent. of all our cases, no entodermal acanthoma has been seen in this species.

Considering all the species, 26 per cent. of acanthomas were situated in the orbital region (i.e. conjunctiva), 11 per cent. in the penis or its sheath, and 23 per cent. in the perineal skin including the lips of the vulva (all caprine cases except two). It is not desirable to give a total figure for the occurrence of acanthoma of the fore-stomachs, since those organs are peculiar to ruminants. (Acanthoma of the oesophageal portion of the stomach of the horse, corresponding to the fore-stomachs of ruminants, is known but has not been seen in this country.) Only in dogs was the buccal mucosa affected and it may possibly be worth while to bear in mind the fact that only in this species do benign contagious neoplasms of the buccal mucosa occur. I do not, however, wish to read anything significant into this correlation.

In the case of the epidermal acanthomas, metastasis is but seldom seen, except in the case of the Angora goat in which it is a frequent occurrence. We have not encountered it in other species. In the case of the entodermal tumours, on the contrary, metastasis was frequent, occurring in three out of six ruminal tumours of oxen and in one omasal tumour of the sheep. The ruminal tumours readily metastasize and also spread by direct continuity, the growths having a tendency to progress intramurally from the mucosa to the serosa, whose lymphatics become permeated; thereafter there is a breaking through the serosa and the formation of continuity growths on the contiguous viscera. Metastasis was not seen in the horse, in the dog, or in the fowl.

(²) It is interesting to note that acanthomas of the rumen, usually considered rather rare tumours and two cases of which have been reported in this country by de Kock and Fourie (1928), are more than half as frequent as those of the orbital region in bovines.

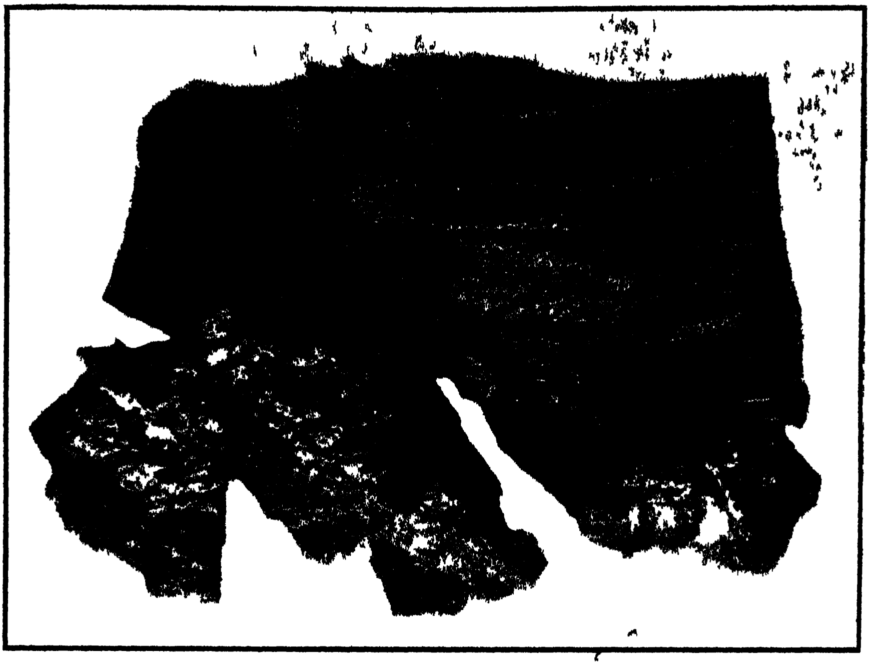

FIG. 14.—Acanthoma of the omaso-abomasal orifice in a sheep (13122, nat. size.)

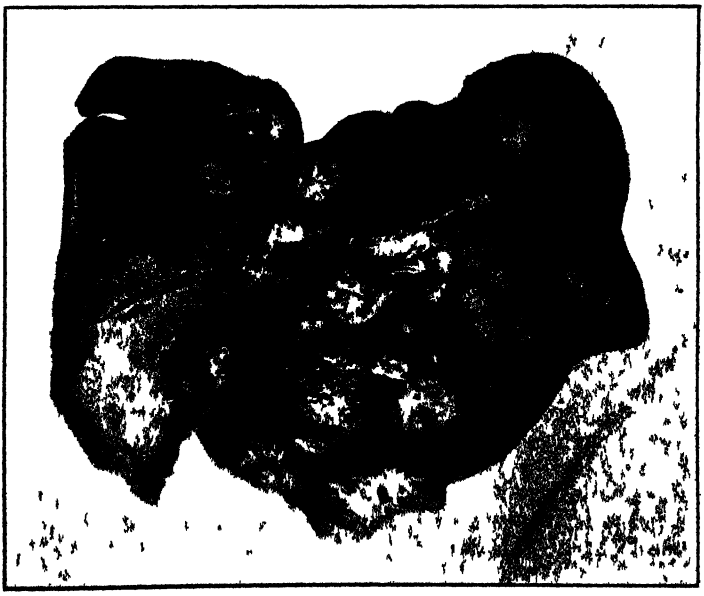

FIG. 15.—Hepatic metastases of the ovine omasal acanthoma shown in fig. 14 (13122, 2/5×)

It has been our experience, in routine pathological diagnosis, that acanthomas are often not recognised with certainty by veterinary clinicians in this country. Clinically they are often confused with superficial actinomycomata, and at autopsy (meat inspection) with visceral actinomycosis. In routine diagnosis one soon becomes alive to the fact that many suspected epitheliomas prove to be actinomycomas and *vice versa*. The older veterinary literature, as is well known, contains many reports of " cancers " of animals which were in reality actinomycosis, and actual endemics of " cancer " causing considerable alarm from the meat inspection and human public health point of view have received prominence in the past. In connection with the confusion clinically with actinomycosis it may possibly be of assistance to the clinician to point out (*a*) that the sites of election of actinomycosis and acanthoma are very different (*vide supra*) and (*b*) that it is often of considerable help to demonstrate " pearls " macroscopically: these bodies can often be recognised with the naked eye. They may, however, be confused with the " granules " of actinomycotic pus; the pale yellow colour of the latter should be remembered as compared with the whiter colour of " pearls ". Giemsa-stained smears will rapidly settle the difficulty in cases of doubt, not only on account of the demonstration of the organisms but also because neoplastic squamous elements are easily recognised in smear preparations. Finally, ulcerating growths in the orbital region of ruminants and equines, on the penis and sheath of equines and dogs (contagious venereal tumour!—actinomycosis being rare), in the perineal region or udder(3) of goats should give rise to a suspicion of acanthoma or of a neoplasm in preference to actinomycosis; while in the case of growths of often somewhat similar appearance in regions other than those election sites the suspicion of actinomycoma may well be strongly held.

Histopathology.—The microscopic structure of typical acanthoma is well known and need only be briefly summarised here. These tumours consist of a connective-tissue stroma which is most variable in its degree of development, in some cases being so prominent as to produce a scirrhous type of growth. This stroma supports nests or strands of cells which in their morphology and arrangement have a resemblance to those of the different layers of squamous stratified epithelium; viz., adjoining the stromal septa is a single layer of vertically arranged cells of the basal type, further from the septa these undergo differentiation into fibrillated (spinous) elements corresponding to the elements of the *stratum spinosum*, while still more " centrally ", i.e. at the parts most remote from the stroma, cornification occurs (*stratum corneum*). The relative development of these different " layers " varies widely, so that in some tumours the basal elements may be very prominent, in others quite inconspicuous as compared with the prickle cells. Typical pearls (i.e. concentrically arranged hornifying elements surrounding centrally placed and fully keratinized cells) are not always developed and the keratinization may only overtake individual cells here and there. It must be noted that the terms " basal cell " and " prickle cell " are used in the commonly accepted textbook sense. Actually the basal cells of the epidermis are also provided with prickles, i.e. cell-fibrils which continue through the intercellular cement substance into the cytoplasm of adjoining cells, as may be seen in properly prepared and stained sections of the skin, a fact which has correctly been pointed out by Haythorn (1931). The distinction is therefore a somewhat inaccurate one.

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(3) Acanthoma of the mammary skin is often erroneously reported as " mammary carcinoma ", a procedure which is to be discouraged.

The mitotic index in the more rapidly growing tumours is high, as much as 13, probably indicating that acanthomas are among the most rapidly growing of all neoplasms. Nucleolar enlargement is a constant feature, n : N ratios of 1 : 4·5 being encountered on occasions.

It is not intended to treat fully of the pathology of all the Onderstepoort tumours in this text, the histopathology of " cancroid " in its typical forms being as well known to veterinary as to medical pathologists. I have selected, somewhat arbitrarily perhaps, a few cases for discussion and description here, because of their rarity or because of special features of the pathology regarding which confusion is likely to exist. Actual difficulties in the recognition of acanthoma microscopically seldom occur.

Melanin-pigmentation of Acanthoma.

Melanin pigmentation of the cells of acanthomas is rare. A pigmented acanthoma has been recorded by McFadyean (1890) in the horse. I find no mention of pigmented acanthoma in the human literature. Thomas, also, in his extensive expetience of epithelioma of goats (among which pigmented epitheliomata are frequent) saw no case in which a tumour of the acanthomatous type bore pigment. We have encountered one case of pigmentation, an acanthoma of the conjunctiva of the horse being concerned. The description of this case follows:—

(*Equine*, 15312.)

The subject was a bay gelding, aged 5 years, from which the specimen, consisting of a finger-tip-sized tumour, attached to the edge of the *membrana nictitans*, was sent in. The neoplasm is of gland-like consistency, white in colour, and presents a lobulated ulcerating surface. Microscopically there is seen a very moderately developed connective-tissue stroma supporting and incompletely separating irregular lobules of neoplastic squamous epithelium. The stroma is in many places densely infiltrated by neutrophiles and erythrocytes. A pallisade arrangement of the neoplastic cells is often very striking, the connective-tissue trabeculae, rich in blood-vessels, being bordered by a layer of vertically radiating cells similar to basal cells and which gradually differentiate into lighter staining areas of flattened and larger cells showing distinct prickles. The n : N ratio is often seen to be markedly increased, being often as much as 1 : 6. The parenchyma, as well as the stroma, especially in the pearls (which may be converted into purulent centres) shows a neutrophilic infiltration, and a rich flora of short bacilli having a coliform morphology is associated with this. Towards the surface of the tumour are seen many elongated or stellate melanophores, having long processes and heavily laden with melanin. Distinct although less heavy melanin-pigmentation is seen in the cytoplasm of the more differentiated tumour cells. Continuity of the neoplastic tissue was traced to a thickened area of the conjunctival mucosa showing downgrowths of the basal layer into the submucous connective tissue (acanthosis). This part of the conjunctiva is itself fairly heavily laden with pigment. At other points the neoplastic cells abut on the epithelium of the mucosa, but here no true continuity is seen, there being no transitions between neoplastic and non-neoplastic cells (in contrast to what occurs in the area of apparently true continuity, where there is a gradual fading of the hyperplastic into the cancerous epithelium). In addition is seen in the *membrana nictitans* a marked hyperplasia of the lymph-nodules of the mucosa, which are occupied almost entirely by the secondary nodules (germ centres) consisting of actively proliferating large lymphoid cells, the smaller lymphocytes being reduced to a narrow peripheral rim; and the *glandula superficialis palpebrae tertium* (sometimes incorrectly referred to as the Harderian gland) is much enlarged, forming a mass measuring 1·5 × ·5 cm., which on microscopic study shows an increase of the interlobular connective tissue and an alteration in the appearance of the alveoli on account of greater prominence of the cell-nuclei, which, although still peripheral in position (as in the normal alveolus) are not compressed against the basement membrane and are spherical or oval in shape instead of crescentic. The ducts are prominently dilated. This glandular mass was actually mistaken in the routine macroscopic examination for a part of the tumour. (We have encountered other cases also of hypertrophic palpebral gland being submitted as neoplastic.) In the substance of the gland are accessory islands of the cartilage of the third eyelid, showing gradual transitions to the fibroblasts (chondroblasts) of the surrounding connective tissue and consisting of young cartilage cells with clear, undegenerated nuclei, and visible nucleoli.

Remarks.—The interesting features of this tumour are:—(*a*) That it was ablated at a sufficiently early stage to allow the actual histogenesis still to be studied: it arises apparently in an acanthotic, melanin-pigmented conjunctival mucosa. [This opinion of the histogenesis is subject to the qualifying remarks we have made elsewhere in connection with what is to be regarded as constituting true continuity as contrasted with apparent continuity (contiguity) and the deductions in respect of histogenesis that may legitimately be made therefrom.] (*b*) The whole question of the occurrence of melanin in both normal and neoplastic squamous epithelium is of great importance in the nomenclature of tumours. Spinous cells containing melanin are among the few melanophorous elements whose nature and histogenesis can be beyond dispute and their occurrence teaches us that there is at least one exception to the theory, often proposed (and reflected in the oncological term " melanoma " and the histological term " melanophore "), that only a special kind of cell can contain melanin. No one would wish the tumour under discussion to be designated as other than acanthoma, merely because melanin is detectable in the admittedly epithelial and obviously spinous cells. It is this consideration which has guided us in the choice of the terminology to be followed in discussing the more frankly melanophorous tumous(*q.v.*). (*c*) The chronic inflammation of the nictitating membrane associated with this tumour is interesting for the hyperplastic processes affecting the lymphoid, the glandular, and the cartilaginous constituents of this structure, but it is not known exactly what respective importance should be assigned to "collateral hyperplasia" under the direct influence of the neoplastic process and to chronic irritation arising on the basis of the infection of the tumour tissue. It is probable that both play a part in the aetiology of these non-neoplastic proliferative changes.

Osteoclasia and Osteoplasia in Acanthoma.

On account of their infiltrative powers, but probably still more because, being ulcerating and exposed tumours which are therefore prone to infection, acanthomas which develop on cutaneous or mucous surfaces in close proximity to bone are likely to have extremely destructive effects on the underlying osseous tissue. Such effects are not seldom to be seen in domesticated animals on account of the neglect which they may suffer when the subject of a tumour. As an example of the extensive skeletal lesions which may ensue the following may be described:—

(*Ovine*, 11859.)

From the autopsy report on a Merino ram, whose age was not stated, we learn that the right side of the face was affected by a large multilobular swelling, foul smelling and fairly hard in consistence, involving also the right eye. On section there was seen a greyish white cut surface with "fine horny granulation". The orbit was partially filled with necrotic material and there was extensive necrosis extending into the ethmoturbinate bones. There was "a softening and a bulging inwards of the ethmoid plate, but no direct affection of the brain. The maxilla is loose on the head".

The museum specimen consists of:—

(*a*) The skin of the right side of the face (see Fig. 16), bearing a bulky ulcerating tumour with necrotic surface, having as its centre the orbital region. The whole is of an irregularly oval outline, measuring 17 × 10 cm. It extends orally on to the maxillary region, ventrally to the angle of the jaw. It consists of about half-a-dozen large lobes, up to 5 cm. in diameter, which are usually also of an oval shape.

(*b*) About half of the skull (right side) sawn in a sagittal plane (see Fig. 17). This shows a large defect, whose centre is the orbital region. The orbital rim is almost completely destroyed, only a small portion of the circumference immediately oral to the horn-core being intact. The zygoma is also almost completely destroyed, only a portion of the zygomatic process of the temporal bone being intact. The zygomatic process of the malar and almost all of the remainder of this bone, as well as the lacrymal, are destroyed. The maxilla has lost its continuity with the bones in the orbital region, there being a large, irregularly circular defect in the medial wall of the orbit, which extends also downwards to cleave through the *pars perpendicularis* of the palatine and forwards involving the maxilla and exposing the maxillary sinus by erosion of both its lateral and its medial walls. The root of the last cheek tooth is completely

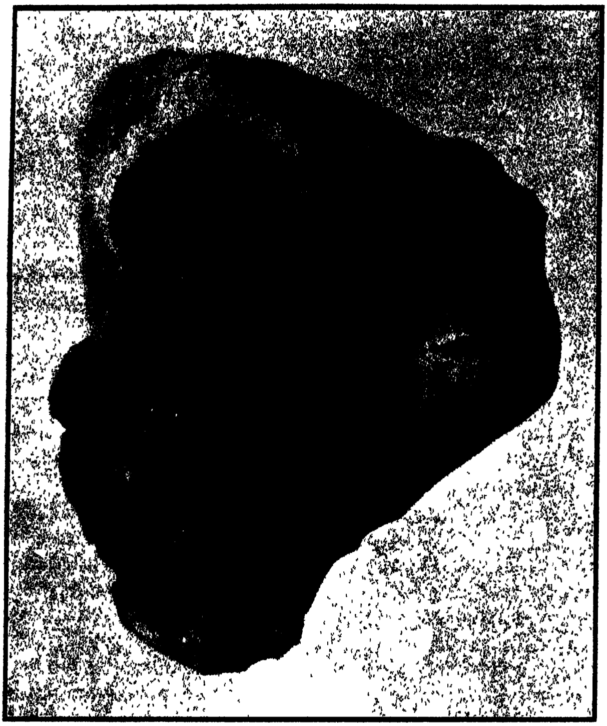

FIG. 16.—Acanthoma of the orbital region in a sheep (11859).

FIG. 17.—Extensive destruction of the bones of the skull by the acanthoma shown in fig. 16 (11859).

exposed. This bony defect measures about 6 cm. in diameter. Above, it exposes the frontal sinus and the supraorbital process has disappeared. The cranial cavity is exposed above and behind the orbit by an irregular defect some 3 cm. across. Only the meninges apparently intervened between the tumour and the brain, resisting (as is commonly the case with yielding membranes) the advancing tissue far better than did the rigid and non-yielding osseous structures. The coronoid process of the maxilla is also for the most part eroded and the oral border of the vertical part of the mandibular ramus is rough and irregular.

Microscopically, the tumour tissue consists of a well-developed connective-tissue stroma enclosing alveoli and elongated strands of atypical squamous epithelium, i.e. a single outer row of cells of the basal type surrounds more centrally placed cells of the prickle type in each strand. Centrally, well-developed, concentrically disposed keratin pearls are often present. Large necrotic areas occur. In the stroma, spicules of newly formed and spongy bone are prominent. In the parenchyma, nuclear irregularities are striking: hyperchromatosis, increase of nucleolar size (n : N commonly 1 : 9), irregularities of nuclear shape. Giant nuclei of the tumour cells may measure as much as 35μ in diameter. Mitoses are frequent (index = 3).

Remarks.—The interest of this case lies in the extensive destruction of bone by an epithelioma which has become extensively infected and necrotic. The well-known resistance of the fibrous membranes as compared with bone to the inroads of the neoplastic process is here well illustrated by the intactness of the meninges although the cranium is destroyed. Microscopically the tumour is characterised by extreme anaplasia of the prickle cells. The osteoplasia in the stroma is to be regarded as secondary to the destruction of bone that is occuring and should not lead to the diagnosis of a mixed tumour (e.g. osteo-acanthoma).

Diagnosis.—Acanthoma.

In connection with new formation of bone as a secondary process in epithelioma, a case in a dog may also be mentioned:—

(*Canine*, 15454.)

This specimen (Fig. 18) is the jaw of an aged, dolicephalic dog whose incisor teeth are worn to the level of the gums. On the horizontal part of the right mandibular ramus is situated an irregularly oval enlargement, 6·5 × 4·5 × 4·5 cm., which is for the most part covered by mucosa, but along the lateral aspect of the molar teeth is a depressed ulcerating area leading to a cavity which involves the roots of the third and fourth cheek teeth. The swelling is most pronounced on the lateral aspect of the alveolar border and extends between and below the molars to the medial aspect of the gum. On the lateral aspect it extends to the level of the ventral border of the mylohyoid muscle, but does not to any extent involve the submaxillary space. The surface is somewhat bossellated, mostly covered by mucosa which here and there shows erosions and haemorrhage. On cutting into the swelling, one encounters in most parts firm white fibrous tissue with bony spicules. Further internally the knife is resisted by solid bony tissue. But around the margin of the depressed ulceration referred to there is a softer, darker tissue of reddish brown colour.

Microscopically, one sees an outer zone of connective tissue, supporting strands of squamous epithelium showing intercellular bridges and various stages of keratinization affecting both individual cells and groups of cells in concentric arrangement. The surface epithelium is acanthotic and shows downgrowths of the rete pegs which may be traced into continuity with the more superficially-lying neoplastic epithelium in the submucous layer. In other parts there is no acanthosis and the mucosa may be thinned and atrophic as if from the pressure from within. Deep to this neoplastic epithelial layer is a rather loose and vascular connective-tissue stroma enclosing irregular centres of osseous tissue, whose osteoblasts are continuous with the surrounding fibroblasts and around which osteoclasts are also to be seen. In the neoplastic epithelium, which is in all stages of differentiation and in which the different cell-nests themselves show varying degrees of differentiation (in some the majority of elements are prickle-cells, in others most of the cells are in the "basal" stage and hornification is but little in evidence"), mitoses are rare.

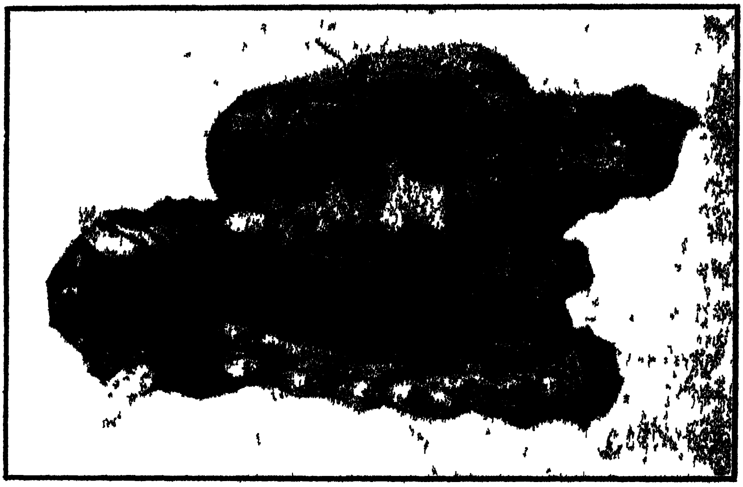

FIG. 18.—Acanthoma of the gum of a dog (15454).

Remarks.—A diagnosis of osteo-acanthoma was considered but discarded because the osseous tissue is to be regarded, not as neoplastic, but as secondary, its production apparently being associated with the resorption of the normal bone.

Diagnosis.—Acanthoma causing osteoplasia of the gum.

The importance of such cases from the diagnostic standpoint is that the new formation of bone, which in pathological as well as in physiological processes accompanies bone-destruction and which may often be a very prominent feature in the bone-eroding acanthomas, may give rise to the erroneous diagnosis " osteo-carcinoma ". This confusion is to be avoided because the osteoplasia is here merely a stromal reaction and of secondary nature, which is initiated (as was proved in the case of the sheep tumour, 11859, by a comparison of the earlier biopsy specimens with those taken at autopsy) only after the destruction of bone has commenced. These acanthomas showing osteoplasia are in no true sense of the term mixed tumours.

An Excessively Keratinised Variety of Acanthoma.

A peculiar type of acanthoma has been noticed in ruminants (sheep) and fowls in South Africa. It is characterised by excessive keratinisation and it may be said to represent the ideal malignant counterpart of the *cornu cutaneum*. These tumours occur, to my knowledge, only on the skin of the fronto-parietal region of ruminants and of the tarso-matarsus of birds, and are not encountered in man, nor in domestic carnivores or Equidae. The sites at which they occur are characterised by being provided with (or being in the region of a transition to) an epidermis which has the normal potentiality of producing horns or scales, and one infers that this fact explains both their species distribution and their location in the body. These neoplasms, in addition to consisting of a typical (although perhaps markedly keratinised), deeply-invasive acanthomatous tissue, form, superficially, large continuous masses of horn which may completely cover the underlying and still actively proliferating cells. The following examples occur in the Onderstepoort collection:—

Case 1 (*Ovine*, 16300).

This has been described by Brown (1935b), who undertook a study of a large tumour which developed at the base of the horn of a sheep and completely lifted the horn from its core, so that the horn ultimately came to form an apical appendage to the tumour, the latter being enveloped in a complete conical cap of soft horn, the product of the neoplasm itself (see Fig. 19). Brown contented himself with a careful morphological study of this tumour, but had no opportunity to correlate it with other cases as constituting a special variety of acanthoma, the reasons for the existence of which have now become clear.

Case 2 (*Ovine*, 6555).

This case was somewhat similar in its pathological features to the previous one. The specimen (Fig. 20) consists of the head of an adult Merino sheep which has a most grotesque appearance owing to the presence of a very large tumour situated on the dorsal aspect of the face and " scalp ", and giving the appearance of a conical hat or helmet on the animal. It measures some 20 cm. in longest (antero-posterior) diameter at its base, 16 cm. in height (from base to apex, externally), and 14 cm. in width (from side to side). It consists of an external cone of soft, lamellated horny tissue which, at the circumference of its base, becomes continuous with the surrounding skin and which is on an average *ca.* 5 mm. in thickness, although here and there it reaches more than 1·5 cm. in thickness;

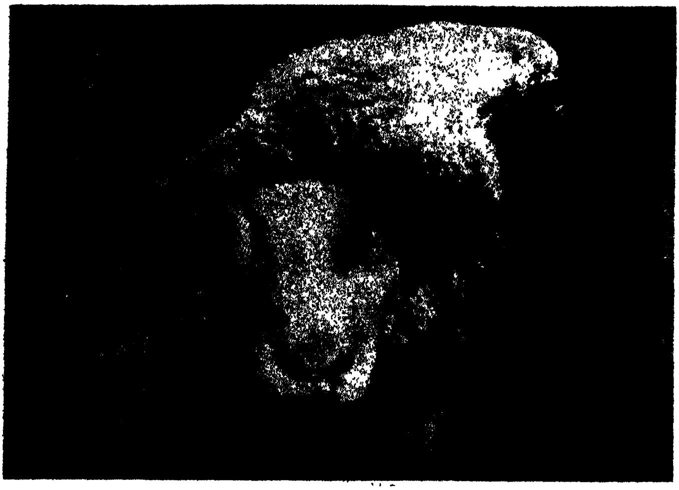

Fig. 19.—Excessively keratinising acanthoma of the scalp of a sheep: displacement of the horn and invasion of the orbit; note the horny covering of the tumour. (16380).—Reproduced by permission of M. H. V. Brown, Esq. and through the courtesy of the Editor, *Jl. S.A.V.M.A.*

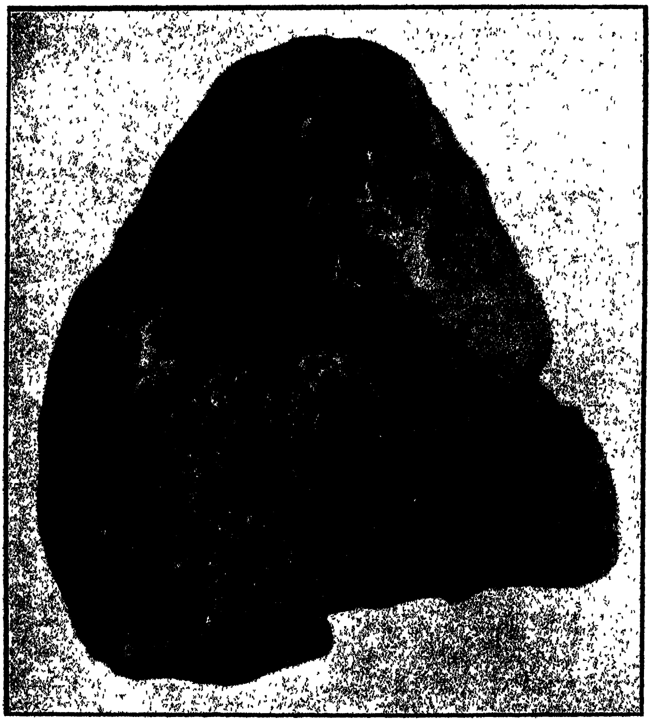

Fig. 20.—Another example of the excessively keratinising acanthoma of the sheep's scalp: Note again the conical shape and the thick horny investment. (6555.)

this hollow horny cone envelops an underlying, solid, conical mass of softer tissue which contains bony spicules. In places the two may be separated by considerable clefts containing structureless, necrotic material. The tumour stretches from (in front) a point 5 cms. aboral to the nostrils to the poll (behind). On each side it extends downwards to the level of the eyes, invading the orbits and displacing the *bulbi oculorum* ventrally. On sagittal section it is seen to have completely destroyed the frontal bone, obliterating the frontal sinus, and the aboral portion of the nasal bone, through which it penetrates to occupy the aboral portion of the dorsal nasal meatus. Only the meninges intervene between the neoplastic tissue and the oral half of the cerebrum, but the *dura mater* as usual provides an effective limitation— (cf. the comments made earlier in this chapter in connection with the superior resistance to the inroads of tumours which the fibrous membranes possess as compared with bone)—and the brain is nowhere invaded.

Microscopically, one sees that the inner, softer mass constituting the bulk of the tumour is composed of typical acanthomatous tissue with very well developed pearls. In sections cut from suitable parts it may further be determined that the superficial cap of horn is proliferated from a layer of basal epithelium which, by invading deeply, is also in continuity with the main underlying mass of acanthomatous tissue. This feature is illustrated in Fig. 21, from a section of the tumour described by Brown. In other parts the two are separated by cavities containing necrotic keratin debris. The microscopic appearances are in all essentials identical with the horny neoplasms of the legs of fowls which are now to be described. The mitotic index is 6.

Case 3 (*Fowl*, 16236).

The subject, a hen of mixed breed, was two years of age and suffered from a growth on the leg which greatly impeded its gait and which was stated to have developed over a period of 9 months.(4) The specimen (Fig. 22) consists of the hock (intertarsal joint) and *pes* of the left side. From the plantar aspect of the hock projects straight downwards a large horny growth, reaching to the ground. It is irregularly conical in shape, having a length of 7 cm. and tapering from a wide (5 cm.) circular base at the hock to a blunt and broken apex which is coated with dirt derived from the soil. Externally it is of a blackish-brown colour and the surface has a scaly appearance. It is much encrusted with a dark (haemorrhagic) exudate. It is dense and slightly elastic, having the appearance and consistency of horn. It gives off the characteristic odour of macerating and decomposing horn. At its base the horny tissue is continuous with a large subcutaneous swelling which encircles the (intertarsal) joint and which causes the diameter of the region to be increased to about 4 cm. This enlargement is due to the presence beneath the skin of a softer, white, infiltrating (neoplastic) tissue in which centres of opaque, yellowish white homogenous material, 1 to 3 mm. in diameter, can be seen. The covering epidermis shows a distinct but irregular margin where the underlying neoplastic mass

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(4) The G.V.O., Aliwal North, who sent in this specimen, was kind enough to supply these particulars.

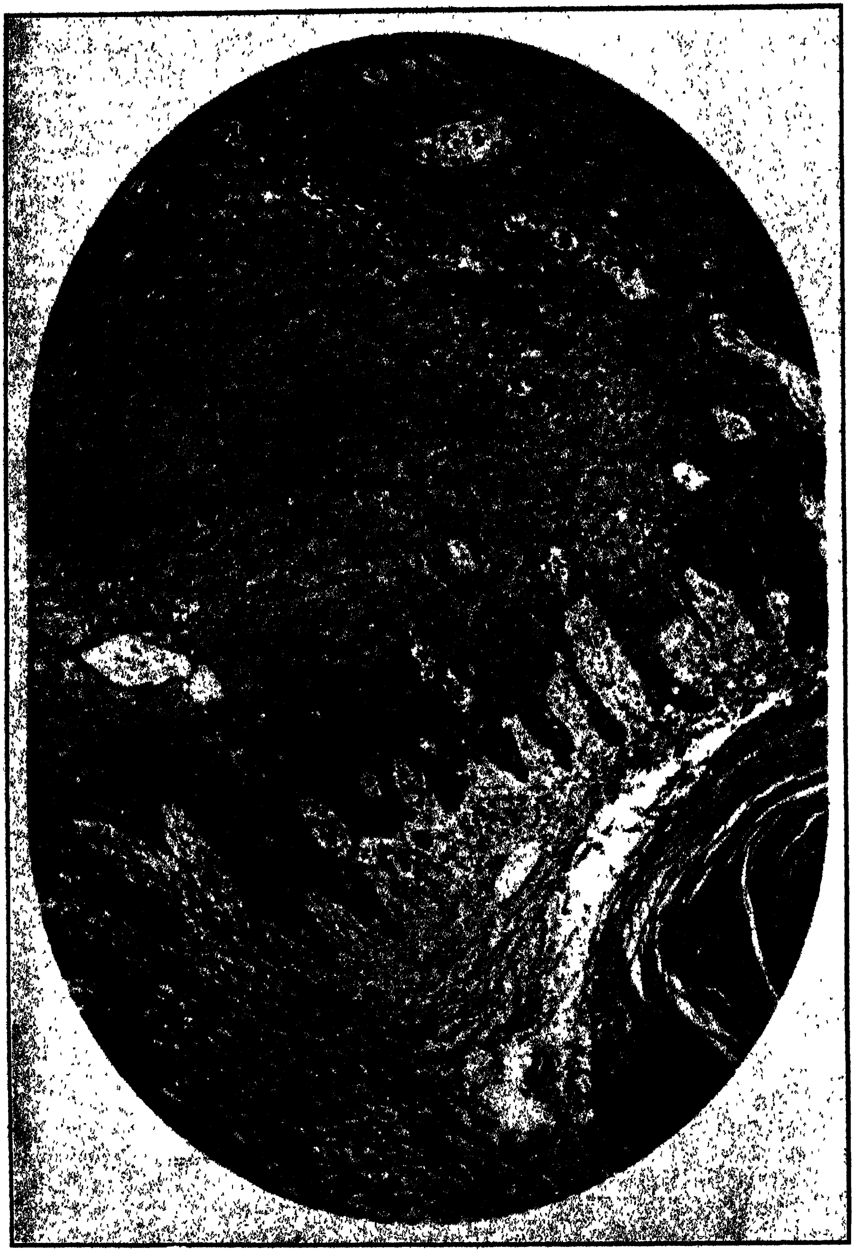

FIG. 21.—Hornifying acanthoma of the scalp of the sheep shown in fig. 19. Above, the covering layer of neoplastic horn; running transversely, the persistent *stratum basale* of the epidermis which (left, below) invades deeply as acanthoma, producing (right, below) very well developed "pearls". (16300; 70 ×).

becomes continuous with the ulcerating horny growth. The metatarsal skin, on its dorsal aspect, shows the hyperkeratotic changes commonly known as " scaly leg " and these scales, at the proximal extremity of the region, continue into a hyperkeratosis of the skin covering the dorsal aspect of the tumour. A distinct, elongated, dorso-ventrally directed, semi-cylindrical fossa runs the whole length of the dorsal aspect of the horny mass to accommodate the metatarsus during extension of the hock. On section, the interior of the horny mass is found to be softer, white, and friable.

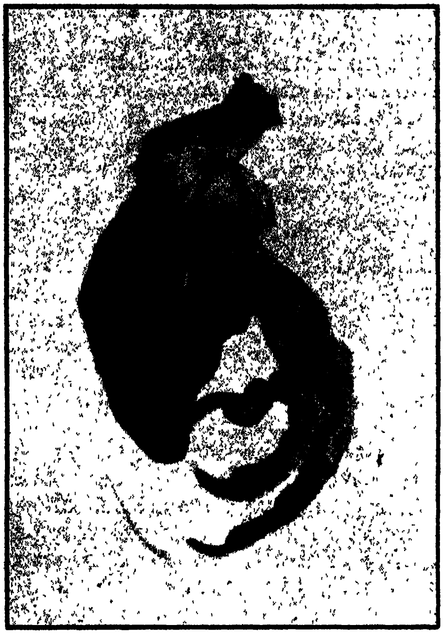

FIG. 22.—Excessively keratinising acanthoma of the metatarsus of a fowl; compare with the cases in sheep. (16236; 1/2 ×).

Microscopically (Fig. 23), sections through the horny mass show this to be composed of a conglomeration of keratin pearls, covered superficially by a haemorrhagic exudate. It is avascular but shows many extensive haemorrhages in which the remains of erythrocytes are still recognisable. Clefts in the horny tissue have a rich flora of cocci. The horn is in the form of parallel lamellae, usually arranged concentrically. Between these masses of horn runs a moderately conspicuous system of collagenous bundles which are quite acellular and avascular. Sections of the neoplastic mass encircling the hock show that this lies beneath a thickened derma and is covered by an epidermis which is for the most part unchanged. In places it infiltrates the derma and approaches close to the epidermis from which, however, it is always separated by the superficial part of the (sclerosed) *cutis vera*. It consists of a cellular and vascular connective-tissue stroma supporting islands and anatomising strands and extensive sheets of neoplastic squamous epithelium with well-marked keratinising tendency. Peripherally, the cell-masses show a layer of the less differentiated cells of basal character separating the prickle-cells from the stroma. Centrally there are pearls in various stages of formation. The larger cell masses are often excavated by cavities containing necrotic debris; this caseous material is largely the remains of granulocytes, which at the periphery may still be intact. Larger cavities containing extensive, layered haemorrhages are lined by non-neoplastic squamous epithelium and are seen to be feather-follicles. In one section apparent continuity is seen between the epithelium of the wall of such a haemorrhagic follicle and the tumour cells: at one point the follicular epithelium is acanthotic, showing a pronounced thickening, about six times its normal width, which is due to a hyperplasia of the *stratum spinosum* as well as to an increase of the basal-cell layer. These proliferating basal cells are in direct continuity with the neoplastic cells at the edges of part of the circumference of the follicular wall which is completely replaced by tumour cells (see Fig. 24). A layer of necrotic tissue separates the living tumour tissue from the conical horny mass, being composed of the remains of leucocytes which form a " reaction zone " abutting on the surviving tumour tissue.

Remarks.—This tumour is noteworthy for its size (reaching the ground) and for the extensive keratinisation which its parenchyma undergoes, especially superficially, so that a conical horny cap covers the underlying and actively proliferating neoplastic tissue. The superficial horn has become necrotic and is obviously in process of being cast off from the living tumour tissue. The tumour structure tempts one to speak of a malignant *cornu cutaneum*. I do not know whether all acanthomas of the legs of fowls show this horn-like growth, but it may be stated that the only other growth in this region of a fowl which we have encountered shows similar features. Histologically although there is evidence which might be taken to support the contention that the tumour arises from the wall of an acanthotic feather-follicle, one must of course remember that it is dangerous to dogmatise in the interpretation of the phenomenon of continuity of neoplastic cells with acanthotic and proliferating squamous epithelium: it is likely, in other words, that we are here dealing with nothing more than a collateral hyperplasia of the follicular wall which preceeds its *replacement* by tumour tissue, the appearance of continuity and gradual transition from acanthotic to neoplastic cells being nothing more than a contiguity. It is not to be thought that the extensive formation of horn represents an attempt to form feather-shafts (cf. the thesis that all pearls in acanthomas represent attempts at hair formation—Boyce, 1892), because feathers, like hairs, are not the product of the follicular wall; but at the same time the marked powers of follicular epithelium to produce horn (see Fig. 32) is well known (see Boyce) under various conditions, and a follicular derivation in this case might be thought to be supported to some extent by the excessive keratinisation which occurred. Further the location is possibly significant, the tumour arising at a point at which the feathers cease and at which anomalous development of the follicles might conceivably be expected to be more likely (cf. cancers occurring at places where one type of epithelium succeeds another, e.g. the natural orifices). This interpretation, of course, is purely speculative, and in my opinion is not the correct one. The site of occurrence may more plausibly be associated with

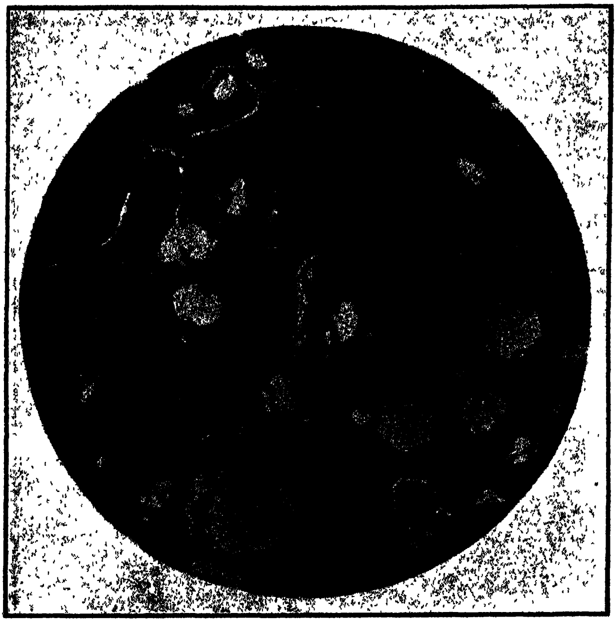

FIG. 23.—Marked keratinisation in the acanthoma of the fowl shown in fig. 22. (16236 ; 30 ×.)

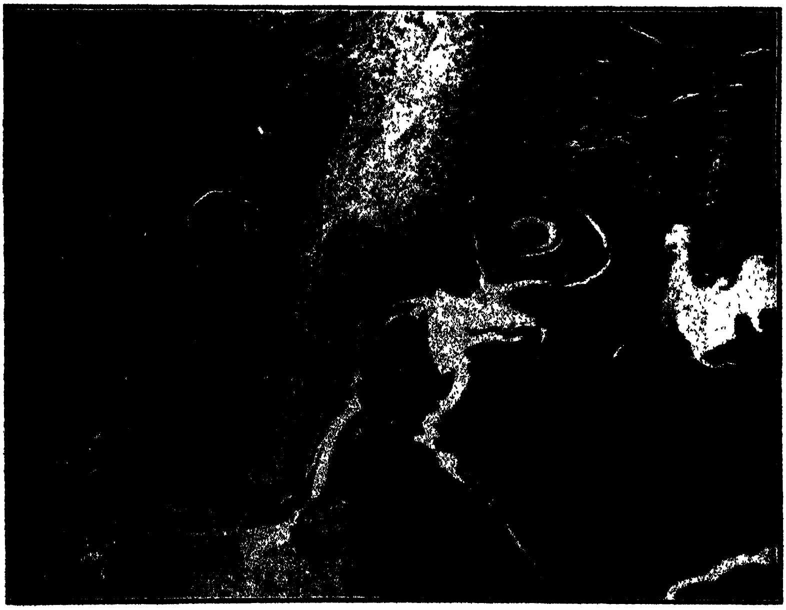

FIG. 24.—Invasive portion of the acanthoma of the fowl shown in fig. 22 : Note (centre) acanthosis of the wall of the feather-follicle and (below and to left of centre) apparent (false) continuity of the follicular epithelium with the neoplastic tissue. (16236 ; 30 ×.)

the constant slight traumata to which the plantar region of the hock is exposed especially at an early age before the habit of roosting is developed. A not dissimilar tumour to this was briefly described by Schlegel (1916) in a fowl. He termed the lesion "*papilloma carcinomatosum*". It was situated also at the plantar aspect of the hock, but somewhat more proximally and the horn-production did not reach the dimensions or assume such a typical conical shape as has been described here.

Diagnosis.—Acanthoma with excessive keratinisation.

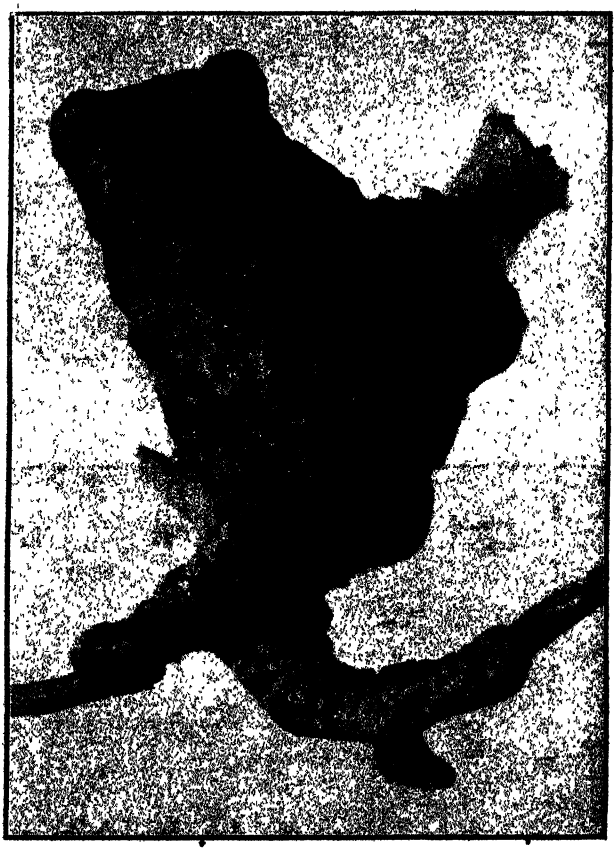

Fig. 25.—Another example of an excessively keratinising acanthoma of the metatarsus of the fowl. (10971 ; natural size.)

Case 4 (*Fowl*, 10971).

This specimen (Fig. 25), the *pes* of a hen, presents a lesion which in all essential respects is identical with the preceding one: a large conical growth projects backwards horizontally from the plantar aspect of the metatarsus. It measures *ca.* 7 cm. from base to apex; and its base, having a diameter of 5 cm., extends almost the whole length of the metatarsus and also passes on to the dorsal aspect of this region. As in the previous cases, it consists of an external, continuous, conical cap of horn which envelops a central, solid, conical core of softer, whitish tissue, and in places large clefts occur between the two.

Microscopically, it is again seen that from a layer of basal cells is proliferated, superficially, a mass of horn which is largely necrotic, while deeply the same layer can be traced into continuity with typical acanthomatous tissue in which pearl formation is very pronounced.

Summary.—A variety of epithelioma has been studied which is highly characteristic both as regards its gross and microscopic pathology and which can best be described as combining the features of acanthoma and *cornu cutaneum*. It occurs in sheep and in fowls, in both of which its location appears to be very specific, viz. the frontoparietal region in the former and the plantar metatarsal region in the latter. These sites of occurrence are to be explained by the fact that this variety of neoplasm can apparently arise only from such ectodermal epithelium as normally has the propensity of undergoing that type of keratinisation which results (in ruminants) in the formation of the horns or (in birds) in the formation of scales.

Remarks on the Histogenesis of Acanthoma.

Regarding the histogenesis of acanthoma, in many cases in the Onderstepoort collection continuity may be traced (as is common) with acanthotic portions of the squamous epithelium in young tumours. In older tumours, the overlying tissues having been destroyed, direct evidence of histogenesis is no longer available. The phenomenon known as collateral hyperplasia (and which may be defined as hyperplastic changes affecting tissues in the close neighbourhood of neoplastic cells) may easily be, mistakenly, considered as evidence of the histogenesis of a tumour. An example has already been given in the discussion of the excessively keratinised epitheliomas of the fowl. In the tumours studied these hyperplastic changes were at times so vigorous as indeed to lead one into considerable sympathy with those who would interpret these pictures as evidence of the spread of tumours by a " conversion " of neighbouring tissue cells. This controversial question will be discussed later. What is here desirable to mention is the light which the study of collateral hyperplastic processes is able to throw on the subject of the potentialities of cells for differentiation and " de-differentiation ". Material suitable for the study of hyperplasia collateral to acanthoma was found especially among the tumours of the Angora goats. The phenomenon has been briefly mentioned by Thomas in his work on the skin tumours of this species, but will bear a closer description:—

(*Caprine*, 15099.)

This Angora goat bore a raised, irregularly oval ulcer of the perineum dorsal to the anus and slightly to the right of the median plane. It measures 2 x 1·5 cm. and protrudes 2 to 3 mm. above the surrounding skin. It is pink in colour with red (haemorrhagic) spots and shows pin-point sized white foci (pearls). It is freely moveable over the underlying tissues. The surrounding skin bears

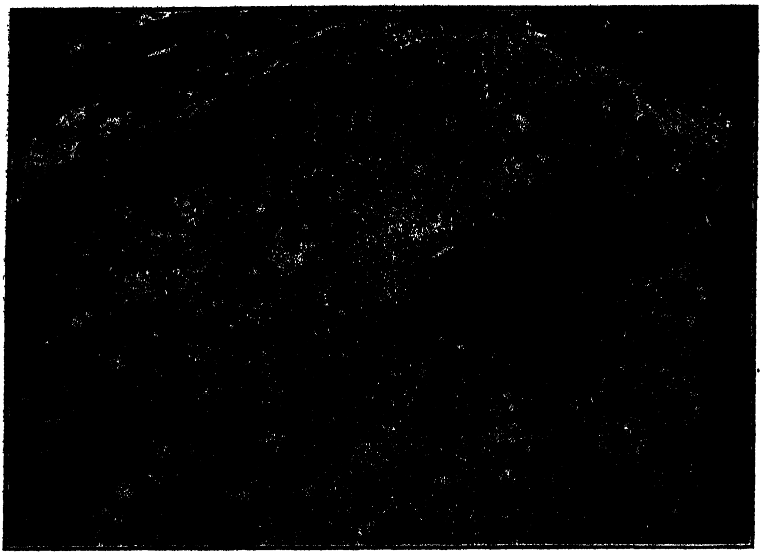

FIG. 26.—Collateral hyperplasia of a sebaceous gland at the edge of a cutaneous acanthoma of the Angora goat: Note proliferation of the basal cells and the formation of a "parakeratin pearl" similar to those that may be encountered in basal-cell epithelioma. (15099; 540 ×).

FIG. 27.—Basal-cell epithelioma of the cat: melanin pigmentation and many "parakeratin pearls" similar to those arising from proliferating sebaceous epithelium as shown in fig. 26. (14021; 120 ×.)

many pigmented spots. Microscopically, the tumour is seen to extend to the depth of the subcutis, but there is not as yet infiltration of the underlying musculature although no encapsulation is present. It consists of a sparse, well-vascularised stroma (infiltrated with lymphocytes, plasma cells, and neutrophiles) supporting large islands and strands of anaplastic squamous epithelial cells which show intercellular bridges and pearl formation. Towards the edge of the tumour the neoplastic epithelium becomes continuous with equally anaplastic cells (cancerous) which are still recognised as being arranged in " rete pegs " invading the derma. This zone of proliferating neoplastic rete pegs is, in the section, sharply limited peripherally from the non-cancerous epidermis by the mouth of a hair-follicle into the cells of which the cancer cells appear gradually to fade. The sebaceous gland alveoli attached to this follicle and bounding the deeper part of the tumour tissue are greatly altered. Differentiation into " adult " sebaceous cells is extremely limited and instead there is a proliferation of the basal cells of the alveoli, which are arranged in a layer several cells in depth and which, more centrally, differentiate into atypical spinous elements. Small " pearls " are also formed in these sebaceous lobules (see Fig. 26). Their significance is discussed further in connection with the basal-cell epitheliomas, in which similar parakeratin pearls may be formed (see Fig. 27). There is a marked increase of the surrounding connective tissue, and some of the sebaceous lobules appear as isolated epithelial islands surrounded by a thick capsule. Mitoses are about four to five times as frequent in the zone of 'proliferating " rete pegs " as in the central part of the tumour. The superficial cells form a partially keratinised layer showing much desquamation and rich vascularisation. The skin immediately surrounding the tumour is non-pigmented.

Diagnosis.—Acanthoma.

The interest in this case lies in the peculiar changes in the sebaceous glands contiguous to the tumour tissue. The phenomena seen show clearly that ectodermal derivatives such as the sebaceous glands can, on stimulation, revert to the less specialised form of ectodermal proliferation, i.e. can form squamous stratified epithelium instead of sebaceous cells. Theoretically, at least, it is therefore not necessary to limit the derivation of acanthomas to the cells of the squamous epithelial surface itself: so far as the potentiality of the cells is concerned, some acanthomas might equally well arise from the elements forming sebaceous glands and hair-follicles. It is interesting to recall here a fact which will be mentioned in dealing with mammary cancers—that even the epithelium of the breast appears to have the power of " de-differentiating " into squamous cells, thereby, like the sebaceous epithelium, recalling its ectodermal derivation. We have found, however, no direct and certain evidence that the glandular derivatives of the ectoderm can give rise to typical acanthomas: the malignant tumours arising from sebaceous glands, while sometimes forming prickle-cells in abundance, also usually show considerable and easily recognisable differentiation into sebaceous cells. The sebaceous epithelioma and the acanthoma are to be regarded as closely allied, but the former tumours should be separated so long as they show a clear distinction of histological characters.

This question is dealt with in greater detail in the discussion of the neoplasms of sebaceous type. Whether the sebaceous gland changes described above are to be regarded as a pure (collateral) hyperplasia or whether, as would appear reasonable to those who urge a spread of cancer by " conversion ", the proliferating cells are rather to be considered as precancerous elements whose fate is to identify themselves with the other neoplastic cells at a later stage is a question which, in the present state of our knowledge, is impossible to answer categorically.

This discussion of the possibility that acanthomas may originate from the elements of the accessory epidermal structures leads one to recall the avian case (16236) of acanthoma already described in which there was continuity of the neoplastic cells with the cells of a feather-follicle. In that case it was conclued that the continuity was a false one so far as its implications of histogenesis are concerned.

Further support for the possibility of the origin of acanthoma from accessory epidermal structures is obtained from two other cases. The first concerns an udder-skin epithelioma of the goat which consists of a mixture of sebaceous epithelioma with typical acanthomatous parts, showing apparently that transitional forms between acanthoma and sebaceous carcinoma occur. [This tumour is of recent acquisition and will not be fully discussed in the present work (caprine, 16239)]. The histological evidence may, however, be better interpreted in the sense that tumour cells derived from the epidermis itself may reflect the pristine potentialities of that tissue by being able themselves to undergo differentiation into sebaceous cells, a view which is further supported by the apparent derivation of sebaceous epithelioma itself from the surface epithelium, as will be described under the sebaceous epitheliomas. The second concerns a dog (canine, 15049) in which an acanthoma was present along with multiple hyperplasias of the hair-follicle-sebaceous-gland complexes which were considered to be of precancerous nature. It was thought likely that the neoplasm had arisen in a similar manner, but the idea is not capable of proof from the material in question. This case also is discussed along with the sebaceous tumours.

It is not intended to discuss the acanthomas further. Our material has been valuable in giving some idea of the species and organ incidence of these tumours and at the same time has led us to consider some possibilities in connection with their histogenesis that we are not as yet able to prove or disprove but which we feel should be borne in mind in the examination of the further specimens that are added to the collection. I have avoided attempting a histological grading of acanthoma, because for most of our cases no treatment was instituted and consequently the accuracy of predictions based on morphological study cannot usually be confirmed. It is, however, customary in routine examination to indicate the fact that a particular tumour has impressed the pathologist as being of a high or a low grade of malignancy. The criteria to be used in the estimation of such degrees of malignancy have been elaborated by Broders (1926) in the sphere of human pathology and doubtless they apply also in principle to the epitheliomas of domesticated animals.

(*b*) BASAL-CELL EPITHELIOMA (*Carcinoma basocellulare*).

Definition.—The general conception of the basal-cell epithelioma is somewhat vague. Under this term Ewing (1928) treats of " reticulated epithelioma " as well as adenoid epitheliomas, including tumours believed to be derived from the sweat glands. More commonly the term is restricted to those tumours which that author describes under the former heading. They are characterized by limited malignancy, being locally invasive but probably never metastatic: over this question a considerable controversy occurs in the human literature, some contending that the fact of metastasis itself is sufficient to disprove a diagnosis of basal-cell epithelioma; and impressive evidence has been brought to show that when a " basal-cell epithelioma " does undergo metastasis it is already changed in type and that prickle-cells, if not demonstrable in the primary, at least characterize the secondary lesion. Some have also tried to avoid the difficulty by setting up a group of tumours (" basal squamous cell epitheliomas ") transitional between basal-cell epitheliomas and acanthomas (Montgomery, 1918). For the purposes of classification of tumours of domestic animals, however, one may say that the basal-cell epithelioma is a locally malignant but non-metastasizing tumour of the skin which is composed of cells resembling the basal-cells of squamous epithelium (or its derivatives) which have a tendency to arrange themselves vertically to the septa of the stroma and especially in elongated and often curved rows whose elements are arranged with their long axes vertical to the length of the strand of cells. Their histogenesis is a matter of controversy.

Occurrence.—Feldman (1932) mentions that his collection contains 3 cases of basal-cell tumours, two from the dog and one from the horse. In view of the fact that in one of the cases (it is not stated which) prickle-cells were seen, the number of genuine basal-cell tumours must be reduced to two, since prickle-cells are, according to modern authorities on the subject, incompatible with the diagnosis of basal-cell epithelioma. Yet, as has been pointed out previously, the normal basal cell shows intercellular bridges, so that the subject becomes very confusing. It is not possible, all the same, to demonstrate intercellular bridges in typical basal-cell tumours and when they do appear it would seem dangerous to class the growth as of basal-cell type merely because of a failure to find epithelial pearls.

Hieronymi (1924) describes a single case in a dog and considers that the tumour is very rare in animals. This authority believes in the histogenesis of these tumours from the accessory epidermal structures, yet he discusses them separately from the tumours of skin glands, and fails to indicate the relationship of the basal-cell tumour to tumours (which he describes) of sebaceous glands and especially of sweat glands. His figures 263 and 264 and 265 (Joest, *Bd.* III pp. 547-8) apparently represent basal-cell carcinoma; and although he diagnoses these as " sichere Schweissdrüsengeschwülste " it is not at all clear on what evidence he arrives at this certainty. His " sweat gland tumours " both occurred in the dog, which is the only domesticated species, so far as I can find, in which unobjectionable cases of basocellular carcinoma have been described(⁵).

In South Africa these tumours were encountered in the dog, the horse, and the cat; and the collection contains as many as 10 examples, 8 of which occured in dogs. In view of this, Hieronymi's view regarding their rarity is in need of modification. Thomas (1929) has described as basal-cell carcinomas certain melanin-pigmented tumours of goats. These neoplasms and the objections to identifying them with the basal-cell tumours are dealt with in Chapter IX.

Pathology.—As is the case in man, these neoplasms of the dog show a marked predilection for the head region, two of our cases occurring in the submaxillary space, one in the parotid region, and one on the cheek, while in the remaining two cases the site was not stated. (Feldman's cases occurred on the face and on the shoulder respectively; and both the tumours of Hieronymi mentioned above were situated on the head, thus further supporting my suspicion that they are no different from basal-cell tumours and should be classed as such.)

In view of the confusion which surrounds the identification of these tumours, it may be useful to give a general summary of the histopathology as based on the study of these cases:—The tumours, as has been said, are found on the head, and, although often almost completely covered by the epidermis, they have a tendency to ulcerate. They occupy primarly the *cutis vera* but extend into the subcutis, in which stratum—in some cases—their greater bulk may be contained (see Fig. 28). Macroscopically they often appear fairly well circumscribed and encapsulated, i.e. they are more or less discrete and rounded masses. Their substance is of a whitish colour, the consistence firm, but they are easily cut.

Microscopically they are characterised by a connective-tissue stroma which is usually a rich one, but which varies considerably, even in one and the same tumour, in its amount and also in degree of cellularity. There is a tendency for the collagen-bundles to be thick, acellular, and almost hyaline in the immediate vicinity of the groups of parenchymal cells. Often the latter may be somewhat shrunken away from the stroma, leaving a considerable space. The parenchyma consists of cells the majority of which have an unmistakable similarity to the basal cells of squamous stratified epithelium. It would give a wrong impression to say that the cells are uniform, close study showing that there are minor variations in size and shape which are associated with a tendency of these cells to undergo a certain amount of differentiation; but the term "uniformity" is useful in indicating the prime characteristic of the histological picture, which is the absolute lack of anaplastic changes. This we consider to be the leading feature of these tumours and one that cannot be too much stressed as a criterion of diagnosis.

(⁵) Wortberg (1928) describes as basal-cell carcinoma a large growth in the shoulder region of a sheep. No photomicrigraphs are given, but from the histological description (especially the presence of frankly keratinised pearls) it would appear that his interpretation would be difficult to defend.

The microscopic picture is one of two chief patterns of cell arrangement:—Firstly (and this one regards as perhaps the most typical), there are elongated strands of columnar elements which stand with their long axes vertical to the length of the strand. These strands are typically one cell-layer in thickness, but often also more. They have a considerable tendency to be curved or to lie in festoon arrangement. This curving when it reaches its fullest degree is responsible for a pseudo-acinous arrangement, which often results in the tumour being mistaken for a glandular neoplasm, especially when examined under low magnification: what actually happens is that the curving of the strands becomes so marked that their ends may almost or actually meet to form loops or rings. There is, however, no true lumen, the enclosed tissue being actually the stroma, which often however is so rarified and delicate in this situation that it is scarcely stained and on casual examination may appear as an open space. The application of connective-tissue stains and close examination under high magnification always shows, however, that " imprisoned " stroma, and not a vacant space, is present within these loops, and when the ends of the loops are not fused it is further seen that this " internal " stroma is continuous with that which supports the " greater curvature " of the strands.

Secondly, there are more massive groups or rounded alveoli of cells, of which the peripheral ones are in all respects similar to those of the strands, again standing vertically with respect to the enclosing stroma; and since the latter encircles the cell mass these peripheral cells must of necessity be placed with their long axes radiating towards the centre of the alveolus. When the alveoli are small, they may be completely or almost completely formed by such a radiating aggregation of the basal cells, there being here again no lumen centrally. These small alveoli, therefore, may be described as rosettes of cells (arranged like the ray-flowers of the inflorescence of a member of the Compositae). In the larger alveoli, the peripheral cells, still only one layer in depth, leave a large central area to be filled and this area is occupied by cells which tend to be somewhat more differentiated. These more differentiated elements are often distinctly spindle-shaped and tend to be arranged in strands or tracts with their long axes parallel to each other but at right angles to those of the peripheral cells. Further, these spindle-shaped cells have a more eosinophilic cytoplasm in which faint fibrillation can be detected on very close study. This fibrillation never results in the production of clear intercellular bridges and the cells are emphatically not prickle-cells: their nuclei are still identical in pattern and appearance with, although perhaps somewhat more elongated than those of the peripheral cells. A further form of differentiation (?) often seen in the centre of an alveolus is a concentric arrangement of the cells surrounding usually a single central degenerate cell showing karyorrhexis and marked hyalinisation of its cytoplasm (see Fig. 27). These structures have been referred to as " parakeratin " pearls, to distinguish them from the fully keratinised pearls of acanthoma, from which they are very different. There is usually but a single layer of curved cells having sickle- or boomerang-shaped nuclei enclosing the central elements which are undergoing keratinisation. These whorls of cells are small, only some 15 to 20μ in diameter and are unassociated with the differentiation of prickle-cells into the large flattened elements with disturbed nuclei seen in acanthomatous pearls. It is quite possible that they arise as much from a mere degenerative change overtaking cells which have no room for growth and which are situated in the centre of the cell mass remote from the blood supply as from any innate tendency on the part of the cells to keratinisation. These small concentric keratinisations are identical with those referred to as accompanying the collateral hyperplastic changes in sebaceous glands (p. 59)—see Fig. 26.

Coming to the detailed morphology of the cells themselves, it may be said that the "vertically" arranged cells of the basal type are quite characteristic. Further details regarding them are that their nuclei are typically elongate-oval, even cigar- or sausage-shaped, their length being often four times their breadth (e.g., 12μ × 3μ). Plumper nuclei also occur (e.g. 6 × 5μ). The nuclear membrane is fine and delicate, and in respect of this as well as of the palely stained and finely divided chromatin, the nucleus may not inaptly be compared with that of a fibroblast. One or two nucleoli are visible, being comparatively very uniform in size and varying, in areal ratio to the nucleus, from 1 : 25 to *ca.* 1 : 50. Larger nucleoli are not seen. Still more elongated nuclei (e.g. 15μ × 2μ) are to be found in the more spindle-shaped cells in the centre of the cell masses. The mitotic index varies from less than 1 up to 4: in the dog these tumours therefore may apparently be quite rapidly growing ones.

From the foregoing description it will be seen that we consider the basal-cell tumours of the dog to have a highly characteristic and specific histology which should preclude their confusion with other tumours. Yet there have occurred not a few instances in which at this Institute the contagious venereal tumours of dogs were mistakenly diagnosed as basal-cell tumours. A further confusion which we must here discuss has resulted from the application by Thomas (1929) of the term basal-cell carcinoma to the pigmented skin-tumours of the goat. I doubt whether this practice is desirable in the present state of our knowledge. Ignorant as we may be of the histogenesis of both these kinds of tumours, it appears to me essential clearly to separate the basal-cell tumours, which do not metastasize and which have a uniform and "monotonous" histological picture, from the metastasizing, melanin-containing epitheliomata which, however much they may deviate in their cytology from acanthomas, are yet not composed of basal cells. There is scarcely a feature in the foregoing cytological description of basal-cell carcinoma which would apply to the far more anaplastic pigmented tumours of the goat. We do not wish to see the term "basal-cell epithelioma" becoming a repository for all kinds of tumours of whose real nature and histogenesis we are still uncertain. Finally, the confusion with glandular tumours has already been stressed in our descriptions and is readily understandable from a consideration of the false glandular appearance assumed by the basal-cell tumours on account of the loop-like arrangement of the cell strands and the rosette-like structure of the cell aveoli. We should unhesitatingly identify with basal-cell tumours those of Hieronmyi's sweat gland tumours which he considers as arising from the alveoli (in contradiction to the ducts) of sweat glands. Whether all basal-cell tumours should be considered as of skin-gland origin is another matter and we do not claim to be in a position to decide that difficult problem.

The Histogenetic Problem.—Few tumours have given rise to such difficulties in regard to the determination of their origin as have the basal-cell epitheliomas, and the problem was made none the easier by Krompecher's conception of a derivation from the basal cells of the epidermis as contrasted with an origin of acanthomas from the cells of the *stratum spinosum*. This original conception has been much criticised on the grounds that (*a*) normally the basal cells of the epidermis differentiate into prickle cells (and finally into cells of the *stratum corneum*) so that there is nothing in the structure of acanthoma to gainsay the assumption that that tumour itself is derived from the basal elements. This argument appears to point very justly to a considerable objection to the theory of duality of carcinomatous tumours arising from the epidermis; and (*b*) that only basal cells are capable of further multiplication and that, therefore, any tumour arising in the epidermis must have this origin. This second objection is without foundation. It is true that normal replacement of the physiological (through desquamation, etc.) wear and tear of the epidermis is accomplished by division of basal (not prickle) cells. But no one who has studied the acanthotic epidermis or the acanthomas can fail to have observed that prickle-cells themselves are capable of active and rapid proliferation. Nevertheless, the difficulty remains that basal cells might well be expected, when they proliferate neoplastically, to undergo the usual differentiation into prickle- and keratinised cells, especially since the basal-cell tumours are considered to grow more slowly(⁶) and, in terms of an accepted generalisation in oncology, should therefore have more tendency (and time) to undergo differentiation than have the cells of acanthomas. If, in other words, we are to regard basal-cell epithelioma as a tumour of the same derivation as acanthoma, we would be setting up a surprising exception to the universal rule that the least malignant tumours are the most differentiated.

It is considerations such as these, as well as the rarity of being able to demonstrate continuity of neoplastic basal cells with the epidermal basal cells and the suspicion that even when such continuity is seen it is a false continuity resulting from nothing more than the establishment of contact between neoplastic and normal cells in the ordinary progress of invasion of the latter by the former, that have prompted many authors to look to accessory epidermal structures as the origin of the tumours in question. Mallory's (1910) theory of origin from hair-follicles, based on a similarity of the cells and the supposed formation of hair-shafts in the tumour tissue, has not yet found general acceptance, although recently Haythorn (1931) has made a powerful plea for the recognition of the basal-cell tumours as derivatives of the hair-follicles or of the necks of the sebaceous-glands, his conclusions depending largely on a more direct histogenetic study.

(⁶) It seems doubtful, in view of the (unexpectedly) high mitotic counts obtained for these tumours, whether this is true for dogs; see however the discussion on the danger of identifying the mitotic index with the growth-rate.

At one time we felt that we had found, in canine material, some evidence in support of the sebaceous epithelial origin of these tumours. This suspicion arose from a case (Canine, 14791) in which in the immediate neighbourhood of a basal-cell carcinoma of the maxillary region were found two warty papules which proved on microscopic examination to be early stages of epithelioma of sebaceous gland origin. These lesions are discussed in detail under that heading, along with other growths of the same type. The inference, a slender one admittedly, was that of three primary (multiple) papules arising as proliferations of sebaceous glands of the cheek, one had progressed to basal-cell carcinoma while the others had remained in an incipient and still recognisably " sebaceous " stage. It may be recalled that Hamdi (1933) (in the sphere of human pathology) has stressed that basal-cell epithelioma arises as a " benign " lesion which remains in that stage for a long time before becoming active. Attractive as it was to consider the basal-cell tumour in the case referred to as a later stage of the sebaceous proliferations which were found in such close proximity to it, this suspicion cannot be justified on the evidence of the above case alone; for in a later case identical sebaceous proliferations were accompanied by *acanthoma* in the same subject; and, further, I encountered fully malignant tumours of sebaceous gland origin, which in no way resembled basal-cell tumours, and which also were accompanied in the same subject by earlier sebaceous gland proliferation of the type previously referred to. It then becomes clear (if I may thus express the dilemma) that if we attempt to " jump out of the frying-pan " of the duality of malignant tumours derived from the epidermis we succeed only in " falling into the fire " of an equally puzzling duality of tumours of sebaceous epithelium.(⁷)

Yet the situation of basal-cell carcinomas, infiltrating far beneath and having no continuity with the epidermis (Fig. 28), greatly favours the thesis of a derivation from accessory epidermal structures, and the fact that the small parakeratin pearls found in basal-cell tumours are morphologically identical with those in hyperplastic sebaceous glands adds strongly to this suspicion.(⁸) The only other possibility, by a process of elimination, seems to be that they may be of sweat-gland origin. For this idea, however, I have been unable to find direct evidence, and in the collection we have no examples of sweat-gland tumours. In most textbooks of human pathology sweat-gland carcinoma is treated as a separate entity. As has been mentioned, it appears to me that as authoritative an observer as Hieronymi has confused sweat-gland tumours with the basal-cell tumours, and there remains a possibility that he may have been led into this (apparent) error because of an essential similarity or an identity between the two.

It would seem that an open mind should be kept regarding the problem until further evidence is to hand.

(⁷) Haythorn's view that it is only the necks or less differentiated portions of the sebaceous glands which give rise to basal-cell tumours offers a way out of this difficulty.

(⁸) The origin of basal-cell epithelioma from sebaceous glands is also very consistent with the absence of this tumour from birds. Yet it is only fair to repeat, when using this fact as evidence, that there are also domesticated mammalian species in which undoubted cases are not on record.

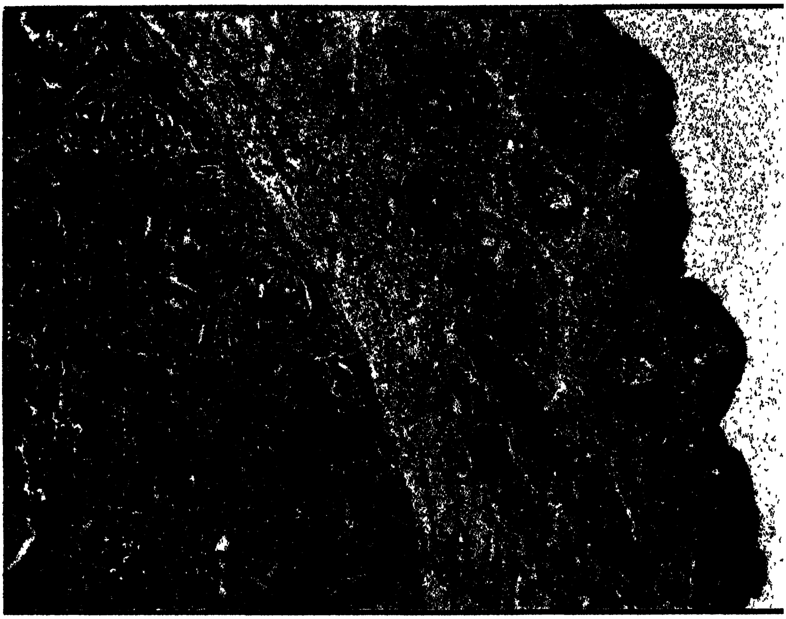

FIG. 28.—Basal-cell epithelioma in the dog: Encapsulation beneath the skin; formation of false lumina. (14791; 30 ×.)

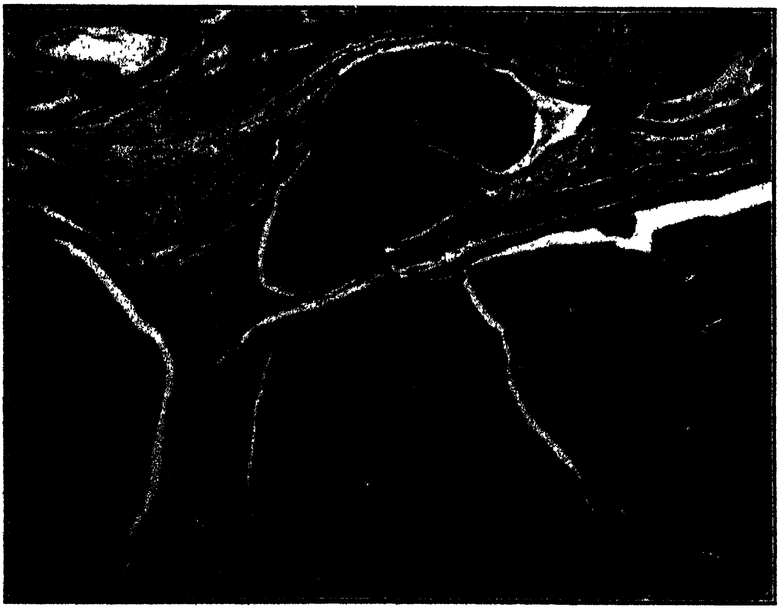

FIG. 29.—Sebaceous epithelioma arising from the peri-anal glands of the dog: Note how the neoplastic tissue invaginates without actually penetrating the thin-walled veins of the stroma. (15902; 33 ×.)

(c) ADENOID EPITHELIOMATA.

Under this category it is proposed to discuss neoplasms which have a resemblance to glandular structures of epidermal origin (excluding the mammary gland), and we are concerned here mainly with neoplasms characterised by derivation from the sebaceous glands or resembling sebaceous glands in their structure. Little is known with certainty of the relations between such tumours and the other epitheliomata. Haythorn and many others consider that the basal-cell tumours are derived from the hair-follicle-sebaceous-gland epithelium, but from a study of these tumours, although final conclusions regarding the histogenesis of the basal-cell tumours cannot be reached, we at least know that they are not the only malignant tumours which have this origin. Further discussion of this group of tumours is better postponed until after a consideration of the individual cases. Two species, the dog and the goat, are chiefly concerned.

(i) *Adenoid Epithelioma of the Perianal Glands of the Dog.*

The collection contains but one case:—

Case 1 (*Canine*, 15902).

This neoplasm was removed, after destruction, from a male Irish terrier, 14 years of age, on which autopsy was not permitted. The specimen consists of the anus and adjacent perineal skin and musculature. The perineum below the anus bears a large, flattened, ulcerating new growth 5 cm. in diameter and 3·5 cm. in thickness (depth) which extends upwards to involve the orifice of the anus.

It is poorly circumscribed and not encapsulated. There are outlying nodules *ca.* 3 mm. in diameter, extending into the anal canal; and the main mass is lobulated, as if composed of an aggregation of nodules of the same order of size. The colour is yellowish white, the consistence firm, and the tissue offers considerable resistance to the knife.

Microscopically (Fig. 29) the tumour is seen to occupy, at its periphery, the deeper portion of the derma and the subcutis, while centrally it ulcerates through the epidermis. It shows a rather regular system of strong and well differentiated collagenous trabeculae which completely or almost completely separate the rounded or polygonal lobules, varying from ·5 to 3 mm. in diameter, which were observed macroscopically. From these trabeculae, which carry the larger blood-vessels, proceeds another system of regular, very delicate, secondary trabeculae mainly composed of thin-walled blood-vessels and capillaries. These vessels have a thin backing of delicate collagenous strands which separate the parenchyma of the lobules into closely apposed, elongated, cylindrical acini, often measuring some 65μ in diameter and over 1 mm. in length. These strands of cells are generally arranged parallel with the nearest primary trabecula bordering the lobule, and are thus straight when the lobule is bounded by straight sides or variously curved where the sides of the lobule are curved. The connective-tissue septa in the more superficial parts of the growth carry, besides blood-vessels, the ducts of sweat-glands, hair-follicles, and sebaceous glands, showing clearly that the stroma of the tumour is largely the pre-existing connective-tissue of the derma. A peculiar feature of the growth is that the lobules are in many cases almost completely surrounded by a venous blood-vessel whose walls have been pushed close together by the expansive growth of the tumour as it invaginates the vessel, and in places there may be complete obliteration of the vascular lumen, the walls being in apposition and the endothelium having disappeared. Such a vessel may receive tributaries from the intralobular stroma. In the sections, the appearance seen is that of islands or peninsulas of parenchyma closely invested by endothelium at their circumference and separated by a narrow space (in which blood-cells are to be found) from an endothelial-bordered primary trabecula: on close examination a thin collagenous backing to the endothelium covering the parenchyma is seen. This invagination of thin-walled veins of the stroma is a striking feature which is present throughout the growth, although not all the lobules show this arrangement; (it is well illustrated in Fig. 29).

Each lobule of the parenchyma has a characteristic structure and is composed of two types of epithelial cells:—

(*a*) At the periphery and bordering the secondary trabeculae is a single row of cells having much the appearance of the basal elements of squamous epithelium. They are somewhat columnar and their long axes are vertical to the direction of the trabecula. The cytoplasm, as in basal cells, is indistinctly stained (pinkish-mauve), homogeneous, and its boundaries not clearly seen. These elements are smaller than the central cells (*b*) to be described below, measuring from 7 to 9μ in long diameter, while their breadth may be gauged from the fact that the nuclei of neighbouring cells are often separated by as small a distance as 1μ. The nuclei are usually distinctly oval, some 6·2μ × 4·5μ, but not infrequently they approach a more nearly spherical shape, being some 5·3μ in diameter. They have a sharp nuclear membrane and stain darkly on account of the presence of many rather coarse chromatin particles tending to obscure the inconspicuous nucleolus. Or these coarse particles may be arranged peripherally, leaving a lighter central area. The nucleolus is usually single, less often double.

There appears considerable variation in these peripheral cells, especially as regards their nuclei, both because varying degrees of pycnosis are common and because of the constant occurrence of forms transitional between them and the central cells to be described.

(*b*) The central cells of the acini are much larger than the peripheral cells. They are polygonal to spherical in shape and rich in a cytoplasm having more distinct outlines than in the case of the basal elements, the boundaries being seen (in Zenker-formol-fixed, paraffin-embedded and haemalum-eosin-stained sections) as fine, deep pink, refractile lines. Since there are, as one proceeds inwards from the basal elements, all degrees of change into the typical central elements, the cells vary greatly in size, from little larger than the basal cells (e.g. 8μ) to very large cells commonly reaching 22 to 26μ in longest diameter. Their cytoplasm (oil immersion objective) is seen to be distinctly cloudy due to closely aggregated, minute, light pink-staining granules having a "soft" appearance, from aggregations of which may occasionally be formed irregularly oval, very inconspicuous, vaguely outlined, light pink-staining, hyaline globules varying in diameter from 1 to 9 μ. This is apparently a degenerative change, since in isolated cells the whole cytoplasm may have undergone this hyaline change and in such elements the nuclei are especially prone to show necrobiotic changes (wrinkling of the nuclear membrane, pycnosis). The cytoplasm further shows fairly numerous rounded vacuoles, measuring up to *ca.* 1·8μ in diameter and reacting to Sudan III, with which stain are discerned all smaller sizes of globules down to the order of size of the pink-staining granules; but when such are reached, the lipoid reaction has already become indistinct. (The basal cells on the other hand give no reaction with Sudan III.)

The nuclei of these central cells are larger and lighter-staining than those of the basal cells. They are oval, measuring 7 to 9μ in long diameter. Many show irregularities of shape (angularities, wrinkling of the nuclear membrane). Their chromatin particles are in general distinctly smaller and less heavily staining (more vesicular nuclei) but, as in the basal-cell nuclei, they have a predilection to be deposited in the peripheral part of the nucleus. The nucleolus shows marked differences: it is often, although not invariably, peripherally located, sometimes in contact with the nuclear membrane; and it is conspicuous and larger, reaching a diameter of 1·8μ. As in the basal cells it may be double. Hyalinised central cells with opaque, deep pink (haemalum-eosin) staining cytoplasm tend to run in strands in the acini, causing a variegated appearance of the parenchyma, a conspicuous feature under low magnification.

In some of the smaller acini, situated at the growing edge of the lobule, differentiation to central cells is slight, and the prominent, closely crowded basal cells occupy most of the acini, leaving room for only a couple of the central cells.

Here and there small whorls of concentrically arranged central cells are formed and fibrillation of the cytoplasm may be seen in such cells although definite keratinisation is absent. Otherwise these whorls to some extent resemble " pearls " and may be termed " parakeratin pearls ". In these cells, too, large fat vacuoles are prominent.

The ulcerating surface shows an exudate of neutrophiles. Mitotic figures are found only after prolonged searching. Occasional haemorrhages occur in the parenchyma. There is no definite encapsulation of the whole growth, but each outlying lobule has its capsule of connective tissue corresponding to the trabeculae separating the aggregated lobules which form the main mass of the tumour.

Remarks.—This tumour closely simulates the morphology of the normal peri-anal glands(⁹) of the dog. Especially regarding the

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(⁹) Anatomical Note.—There exists much confusion among veterinarians and in the literature regarding the glands in the neighbourhood of the anus and it is necessary to state that the *peri-anal glands* are modified sebaceous glands which must be distinguished from: (1) *anal pouch glands*, which lie in the walls of the *sinus paranalis* (anal pouches) and which are compound glands morphologically related to sweat glands but producing a fatty secretion; (2) *sebaceous glands* occurring especially in the neck of the wall of the anal pouch and around its opening; (3) *anal glands*, situated in the submucosa of the *zona columnaris* of the anus and extending also into the muscularis. These are alveolar glands and have a fatty secretion in the dog; (4) *the sebaceous and sweat glands of the zona cutanea* of the anus. (Ellenberger and Baum, 1921.)

cytology, the correspondence is very close. There is a greater crowding of the basal cells and the tendency to form whorls of fibrillated cells not seen in the normal gland. In cytological details, including nuclear appearance, size, and nucleolar-nuclear ratio there are no obvious departures from the normal. In classifying a growth of this type we have to consider the following points:—The close adherence to the normal cytology and the absence of encapsulation constitute features reminiscent of mere hyperplasia. However, the ulcerative nature of the growth and the magnitude of the process as well as the absence of excretory ducts would not justify such a diagnosis. An unqualified diagnosis of malignancy (carcinoma) is also not to be thought of on account of the close reproduction of the normal architecture, the normality of the cells themselves, the very low mitotic index, the absence of increased nucleolar size, and the absence of intravascular invasions. Further it is somewhat difficult to evaluate the relative importance, in the ulcerative process, of the actual invasive tendency of the tumour and the traumatic influences to which the covering skin of a perineal growth in the dog would be especially liable on account of irritation and the response of the subject thereto. The diagnosis of adenoma remains to be considered and this is the term which has usually been applied to these tumours, which appear to be fairly well known in dogs—(Joest, *Bd.* 1, S.748—excellent macroscopic illustration). While in many respects being a suitable term by which to designate such a growth, " adenoma " fails to indicate the porgressive invasive growth and the ulcerative tendency of these tumours. It appears to me that in naming the tumours arising from squamous epithelium and its immediate derivatives in mimicry of terms (adenoma, carcinoma) essentially designed for tumours of columnar epithelial surfaces and their glandular derivatives we succeed in a simplification only at the expense of loss of clarity in our meaning. This fact has of course been widely recognised and is at the bottom of the adoption of the term " epithelioma "—itself perhaps an unfortunate choice, but by now too firmly established to make a change easy. The best designation for the tumour under discussion appears therefore to be " adenoid epithelioma "; the merits of this term depending on its emphasis on the ectodermal derivation and affinities, the essentially glandular nature of the growth, and an absence of a dogmatic indication of whether the tumour belongs more to the benign or to the malignant neoplasms.

Diagnosis.—Adenoid epithelioma (" adenoma ") arising from the perianal glands.

Occurrence of and Literature concerning Epithelioma of the Perianal Glands of the Dog.—The case described is the only one to our knowledge encountered in South Africa. Although Feldman states that " . . . the perianal glands exhibit a special predilection for these growths (adenomas) ", yet he has not apparently encountered a case himself, and although we must accept this statement and it is probable that they ought to be regarded as common tumours, yet the incidence in this country appears to be low. (Joest, *Bd.* 1, pp. 747-50) has given a good short description of the tumours in question, which were first described by Siedamgrotsky (1877), and indicates that they are of frequent occurrence. The tumour illustrated by him in is in its general morphology very similar to the one we have described, and this author leaves open the question of whether the term adenoma or adenocarcinoma should be applied. He indicates that these growths usually behave in a benign fashion, but that metastases and recurrence can occur " *wenn die Geschwulst . . . die Character eines Adenokarzinoms besitz* ". It is evident, then, that various grades of malignancy occur and that it is advisable to indicate in the diagnosis (as we have done above) whether the tumour is more related to adenoma or to carcinoma. Ball (1926) (*cit.* Dupas, 1928), in a work not available in South African libraries, is said to devote a whole chapter to the discussion of these tumours and to distinguish also between " adenoepithelioma " and the " metatypical form ". Dupas (1928) gives a close description of the pathology of a case of the malignant type encountered by him but which has not been observed in this country (although highly malignant tumours of sebaceous type have been seen elsewhere in the dog, e.g. on the cheek). This frankly malignant variety, of more atypical histological structure, is, presumably, far rarer than the non-recurring and non-metastasizing kind, only three cases of the former having been encountered by Ball. Valade (1934) has also indicated the common occurrence of these tumours, and he discusses their nature in some detail. Having (apparently) observed only the malignant variety, he makes the misleading generalisation that histologically the structure is incontestably of cancerous nature and in his description the anaplastic changes are given much prominence.

(ii) *Adenoid Epitheliomas arising from (other) Sebaceous Glands.*

In dogs we have not infrequently encountered small nodules of the skin, usually occurring in multiple form, of which I can find no really clear description in either the human or the veterinary literature. The following cases are to be described:—

Case 2 (*Canine*, 14971).

This specimen concerns two papules found in the skin of the maxillary region in close association with a lesion, already referred to, which proved to be a basal-cell carcinoma. Indeed, they were removed surgically at a later date than and after the diagnosis of the tumour mentioned because of the likelihood that they were the precursors of similar tumours. The nodules were two in number, of a pale yellowish colour and slightly raised above the surrounding skin. They presented fine markings suggestive of lobulation, moved with the skin (not being attached to the deeper structures) and measured 2 and 3 mm. in diameter respectively.

Microscopically, these nodules are seen to be due to circumscribed but not definitely encapsulated proliferations of sebaceous glands. There is a marked hyperplasia of the basal cells of these organs accompanied by most imperfect differentiation, so that the alveoli are formed by but a few sebum-containing elements surrounded by many layered basal epithelium in which mitotic figures are frequent. Occasionally there is also a slight infiltration of neutrophiles into the epithelium and in the adjacent parts of the corium.

Remarks.—Lesions of this nature are presumably often classed as sebaceous "adenoma". But the process in the stage described is essentially a hyperplasia of pre-existing structures. The close topographical association with a (fully developed) basal-cell carcinoma provides strong evidence that these papules may be the precursors of such tumours. Their high mitotic index indicates that they are exceedingly rapidly growing and it is probable that such lesions should be regarded as precancerous if not actually as early stages of malignant neoplasms.

Diagnosis.—Multiple sebaceous gland hyperplasia, probably to be regarded as precancerous and possibly leading to the formation of basal-cell carcinoma or adenoid epithelioma.

Case 3 (*Canine*, 15952).

The specimen consists of three pieces of skin removed from an eleven-year-old male cocker spaniel at the time of destruction:—(*a*) Skin from the forehead shows a thick raised plaque, standing some 4 mm. above the surrounding surface and measuring 2·3 cm. in diameter and 1 cm. in thickness. It is circular and discoidal. On section the cut surface is white, of firm consistence, and somewhat friable (fixed specimen). The surface is partially covered by a hard brownish crust. (*b*) and (*c*) Two pieces of skin from the arm and leg respectively. (*b*) One shows a small, broadly pedunculated growth, 5 cm. in diameter and having a granular surface. On section it is seen to be composed of polygonal or rounded lobules 1 mm. in diameter. (*c*) The other bears a similar, but smaller, whitish nodule measuring ·3 mm. It has a somewhat acuminate shape and a lobular appearance is not seen. It is covered by a haemorrhagic encrustation.

Microscopically:—(*a*) The growth from the frontal region (see Fig. 30) shows a stroma of coarse trabeculae of connective tissue which give off finer septa completely dividing the parenchyma into polygonal lobules or elongated strands. In many parts this stroma is fairly cellular (fibroblastic) and it also shows a moderate lymphocytic infiltration. It carries a generous vascular supply. The parenchyma is composed of several cell varieties, all of which are clearly modifications of one and the same type and between which transitional forms are readily to be seen:—(i) The greater number of the cells are oval or columnar elements with indistinct cytoplasmic outlines and elongate-oval nuclei and have a distinct tendency to be arranged vertically to the interlobular septa; or in long rows of vertical elements where the parenchyma is arranged in narrow strands some two cells in thickness. The nuclei (usually some $14 \times 10\mu$) are rather heavily chromatic, being filled with numerous coarse to fine chromatin particles. The nucleoli are usually two in number and are considerably obscured by the chromatin and are not prominent (*ca.* $1{\cdot}5\mu$ in diameter—i.e. a n:N ratio of some 1 : 60). These elements are thus of the basal type but are not normal basal epithelial cells morphologically. (ii) In many places these cells go over into spindle-shaped elements having a somewhat larger amount of cytoplasm and showing "clearer" nuclei, i.e. although the chromatin particles are actually coarser they are less numerous and on this account, as well as because of an absolute increase in size (*ca.* to 2μ), the nucleoli are somewhat more prominent. (iii) This type consists of flattened cells of squamous character having definitely vesicular nuclei, in which relatively few chromatin particles are present, and prominent nucleoli (4μ). The nuclei of these cells are larger, measuring $38 \times 14\mu$. Rarely, traces of intercellular bridges are seen. (iv) The cells described under (iii) may produce definitely keratinised elements arranged concentrically to form small pearls. (v) Lastly, there are large polygonal elements filled with fatty globules and arranged singly or, more often, in groups. Their nucleoli often measure $3{\cdot}5\mu$. Eventually, in these cells the nuclei become shrunken and lie centrally in the fat-filled cytoplasm. These cells are often closely associated with the masses of squamous elements so that hornification and sebaceous secretion proceed side by side in neighbouring cells; and where such cells have (as is often the case) a concentric arrangement, peculiar "vacuolated pearls" result, i.e. partially hornified cyst walls filled with sebaceous material and cell debris. Such cystic cavities are fairly frequent in the tumour and vary from the diameter of a single cell to 100μ. Cysts also occur which are lined by the as yet non-keratinised elements described under (ii). Mitotic figures are fairly frequent, but no abnormalities of mitosis are noticed. Haemorrhages may occur between the tumour cells. Superficially the growth presents an ulcerating surface covered with purulent exudate, and neutrophiles infiltrate the stroma in the neighbourhood.

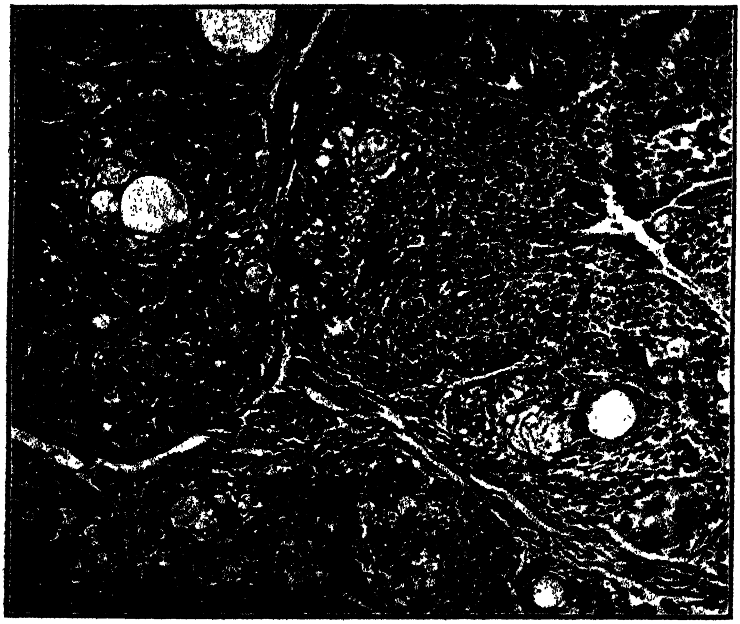

FIG. 30.—Detail of the structure of the adenoid epithelioma (lesion *a* in the text) of the dog: Note among the undifferentiated cells the groups of more differentiated elements which are in part keratinised and in part sebum-secreting, resulting in formation of small cysts. (15952; 110 ×.)

(*b*) This nodule (Fig. 31) is situated in the cutis and is covered by a highly acanthotic epidermis, which it raises prominently above the surrounding surface. Of this cutis the *stratum corneum* is considerably increased in thickness and the *str. granulosum* and *str. spinosum* are greatly increased. The rete pegs are most exaggerated in breadth and depth and these downgrowths merge everywhere into hyperplastic sebaceous alveoli which, demarcated by fine strands of connective tissue and grouped into lobules by coarse strands (apparently the pre-existing connective tissue of the *cutis vera*), constitute the actual bulk of the nodule. The lobules mentioned consist of a single peripheral row of basal cells within which are solid masses of sebaceous cells not differing obviously from the normal elements of sebaceous glands. Associated with these sebaceous lobules are the aforementioned down-grown " rete pegs " which are often branched and hollow, i.e. forming ducts for the glands and in which may also develop cysts filled with keratin and lined by all the layers seen in a normal epidermis, including a prominent *stratum granulosum*. Within the lobules occur also small cysts lined by flattened keratinised cells, backed by a layer of spindle-shaped elements showing distinct epithelial fibrils, and containing sebaceous material and cell debris. Mitoses occur in the basal cells of the sebaceous alveoli, but are not frequent, being about as numerous as those to be seen in the basal layer of the acanthotic epidermis. There is no special encapsulation from the rest of the *cutis vera*, and on the other hand no evidence, as yet, of distinctly invasive growth.

(*c*) Sections of this nodule (Fig. 32) show the following:—The epidermis is affected by pronounced hyperkeratotic and acanthotic changes and a few of the papillae of the *cutis vera* are greatly elongated, forming tall, acuminate outgrowths covered by epithelium and matted together by an exudate of horny debris mixed with red cells and neutrophiles. At the edges of the lesion the hair-follicles show thickening of their walls and their mouths are filled by horny plugs (the *hyperkeratosis suprafollicularum* of dermatological pathology). In the nodule proper (responsible for the bulk of the enlargement) are two epithelial masses which are interpreted as altered hair-follicles: in serial sections both are shown to be continuous with the epidermis by mouths which are filled with purulent exudate and horny debris. The epithelial proliferations themselves lie beneath the epidermis from which (except by a study of the serials) they might be thought to be isolated by the connective tissue of the corium. The one is composed of all the layers of the epidermis, but is altered by acanthotic changes and encloses the central lumen of the follicle. This contains horny debris, which, nearer the surface, becomes mixed with a purulent exudate. Internally this epithelium is markedly hyperkeratotic; externally the margin shows a number of blunt, branching, proliferating masses of epithelium comparable to hyperplastic rete pegs. The other follicle shows more advanced changes: the same horn-plugged lumen with cellular exudate is present, but there are pronounced proliferative changes of the epithelial wall, which exists as a number of typical horn-cysts lying peripherally and connected to the centre by strands of proliferating cells among which mitoses can be found and most of which are of the basal type. The whole is well circumscribed.

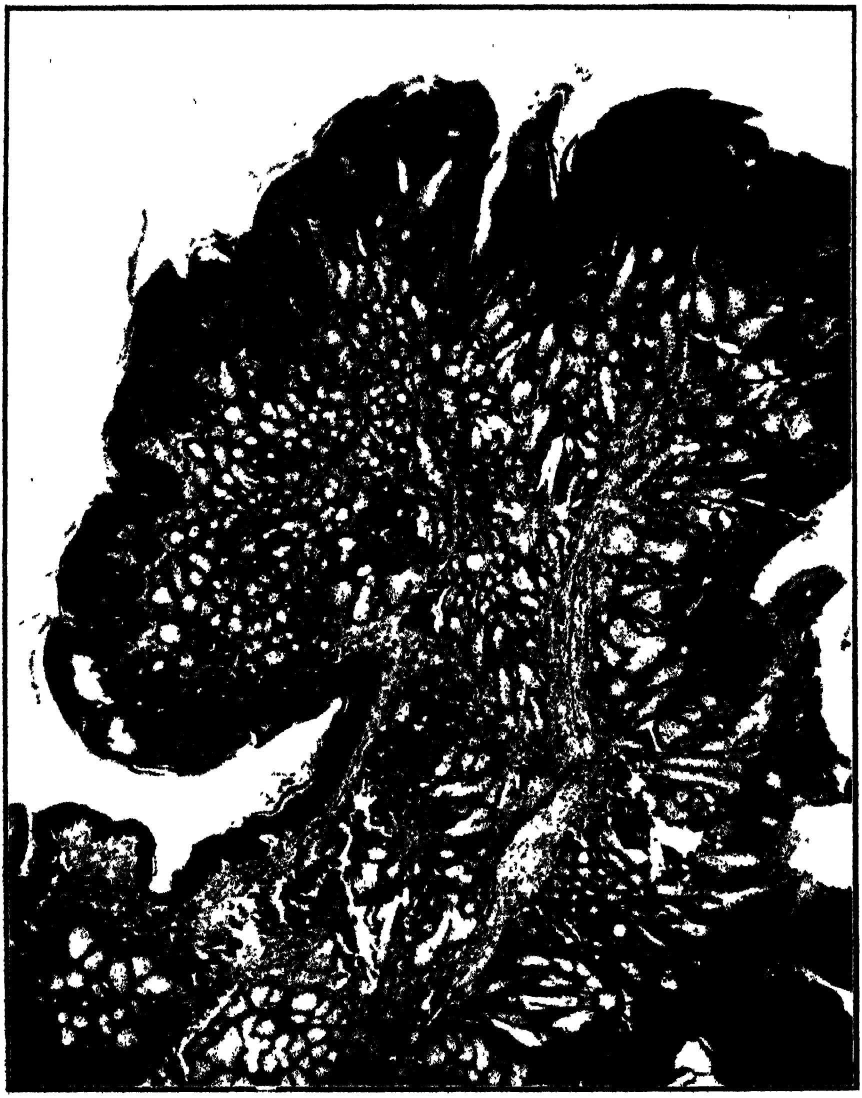

Fig. 31.—Small sebaceous epithelioma of the dog (lesion *b* of the text.) (15952; 30 ×.)

Remarks.—Although the actual histopathological processes involved are clear, the greatest difficulty lies in the classification of the lesions described. The first lesion is an epithelioma which combines the features of basal-cell proliferation (basal-cell epithelioma), sebaceous epithelioma, and adenoid cystic epithelioma. On account of its ulcerative nature and evidence of rapid-growth it cannot, even at its present stage, be regarded as other than a malignant growth. Somewhat similar lesions of the dog have been designated by Hieronymi (1924) as adenoid cystic epithelioma of Brooke (a lesion of the human subject), but these do not seem to have reached the degree of malignancy of which this growth gives indications. Its pathology may be summarised as follows: an ulcerating growth, non-encapsulated, but (as yet) confined to the skin, composed predominantly of neoplastic basal epithelium rich in mitoses and showing a tendency to differentiate into both sebaceous cells and flattened cells forming horny cysts. There is no fundamental histological difference in type between this lesion and Brooke's epithelioma of man. However, it is probably not wise to take over such a term from human pathology unless the lesions are actually identical in their behaviour as well as in their pathological anatomy.

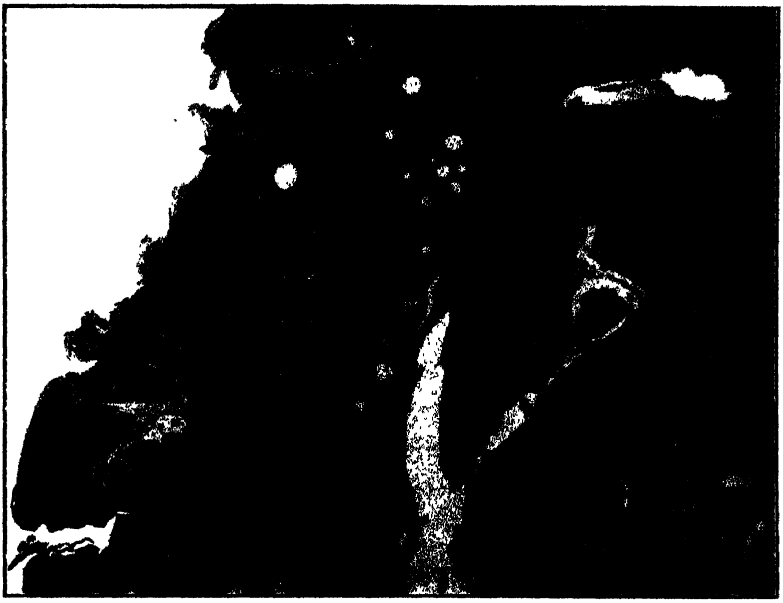

FIG. 32.- An early epitheliomatoid lesion in the dog (same subject as figs. 30 and 31); (lesion *c* of the text): Proliferation of the walls of two hair-follicles. (15952; 30 × .)

The second lesion described shows evidence of a new formation of atypical sebaceous glands from an acanthotic epidermis, through downgrowths of rete pegs, which differentiate at their distal ends into sebaceous cells and also have a tendency to form cysts and to become keratinised, while their necks become hollowed to provide ducts to the glands. The tumour is a more benign counterpart of the first lesion. It would probably (loosely) be called a " sebaceous adenoma ".

The last lesion is peculiar, and no pathological process embodying all the features seen could be found described in either human or veterinary dermatological texts. It has many of the features of the lesion described in human dermatology as *hyperkeratosis follicularis vegetans*, consisting essentially of a proliferation of hair-follicle walls with excessive formation of keratin which blocks the mouths of the follicles, and it is associated with a purulent infiltration (probably secondary). But added to this is the marked tendency to the formation of horny cysts within the acanthotic follicular wall. These changes in the hair-follicles are associated with alterations of the epidermis having to some degree the character of acuminate condyloma.

One is tempted to assume that all these lesions are but variations of one and the same process and that a minute sub-division in strict accordance with the histo-pathological anatomy may result in an artificial differentiation between them. All three, but most certainly the first, are to be regarded as pre-cancers in the best sense of that not unobjectionable term, viz., they are lesions which, if not interfered with, would (one feels with a high degree of conviction) develop into frankly malignant tumours. What seem more important to us than this consideration, however, are the histogenetic principles which are suggested from a study of these apparently little known cutaneous lesions of the dog: proliferations derived from basal epithelial cells may grow either as undifferentiated basal cells, as hornifying squamous elements forming intercellular bridges and horny cysts, or as sebaceous gland cells. What then happens to the old distinction (Krompecher) between the potentialities of basal and spinous cells respectively? One can no longer doubt that from basal epithelium, in neoplastic grades of proliferation as well as in normal organogenesis, various cell types may arise on the basis of the intrinsic potentialities for differentiation possessed by these cells. For the histogenesis of three types of epithelioma—acanthomas, basal-cell tumours and adenoid tumours—this principle appears to us to be of the first importance, showing that dogmatic statements implying an exclusive origin of any of these tumour types from a single site or cell type are to be avoided.

Diagnosis.—The strict histo-pathological diagnosis of the three lesions described would appear to be (i) adenoid cystic epithelioma [sebaceous adenoid carcinoma (?) in early stage]; (ii) sebaceous adenoma; and (iii) *acanthoma adenoides cysticum* (Unna) in early stage. Together they may be classified as a case of multiple adenoid epitheliomata.

Since the above cases were described, a case of frankly malignant sebaceous epithelioma of the face with regional lymph-gland as well as pulmonary metastases has come into our hands, but unfortunately too late to be included here.

Case 4 (*Canine*, 10223).

This was a large growth (Fig. 33) removed from the "back" of a dog at operation (10). It weights approximately 890 gms. and is of flattened-hemispherical shape (bun-shaped). It measures 13 cm. in diameter and 7 cm. in height. It is covered by skin which bears rather widely separated tufts of hair, in places it is actually devoid of hair. These tufts, reddish-brown in colour, sprout from the follicles as groups of six to a dozen hairs, each tuft having much the appearance of a camel-hair brush. The skin is pigmented, being in the formalin-fixed specimen of a slate-blue colour. Over the base or underside of the tumour is seen the (surgical) incision through the broad peduncle some 8 to 9 cm. in diameter and formed by a highly adipose subcutis. The actual new growth lies immediately below the epidermis, which is apparently unthickened. From here to a depth of 3 cm. is seen on section a layer of tough, mottled greyish and light yellowish tissue, limited deeply by the subcutis which is heavily laden with fat. From the subcutis this altered *cutis vera* is not encapsulated, but the line of limitation is quite sharp. At the edges, this altered derma is curled in on all sides towards peduncle, gradually diminishing in thickness. For the most part the covering epidermis is smooth but here and there it is roughened by soft papules, ·25 to ·5 cm. in diameter, standing slightly above the surface. The whole growth, with its curled-in borders and prominent tufting of the hairs has often been likened to a hedgehog by visitors to the Onderstepoort museum.

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(10) The Department is indebted to P. L. le Roux, Esq., M.R.C.V.S. for this tumour.

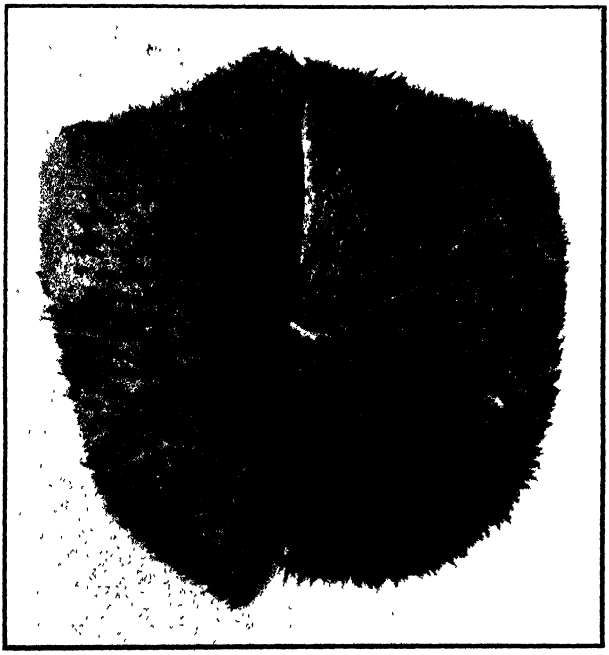

FIG. 33.—A large lesion of the skin of the lumbar region of a dog consisting in sebaceous gland hypertrophy and hyperplasia (sebaceous adenoma). (10223; 1/2 ×.)

Microscopically, the picture seen (Fig. 34) is a complex one at first sight, the specimen having remained for some years undiagnosed and indeed having been regarded as in the province of teratology.

Reduced to its essentials, however, the histology may be described as follows:—The tumour consists of a greatly thickened derma, this thickening being caused by two chief factors: (*a*) a huge increase in collagenous bundles, this connective tissue being on the whole poor in fibrocytes; (*b*) a most striking " hypertrophy " and " hyperplasia " of the sebaceous glands: these glands lie for the most part deeply in the *cutis vera* and are much lobulated. They are supplied by ducts which are often branched. The ducts open into hair-follicles and also directly to the surface epithelium. Apart from their exaggeratedly rich lobulation, the glands (i.e. their individual lobules) show as a rule no striking departure from the normal. In places, however, there is also a proliferation of their basal cells, which then show but little tendency to normal differentiation: thus arise solid lobules of basal cells. The ducts often show exaggeration of the normal keratinisation (sebaceous duct hyperkeratosis) and this,

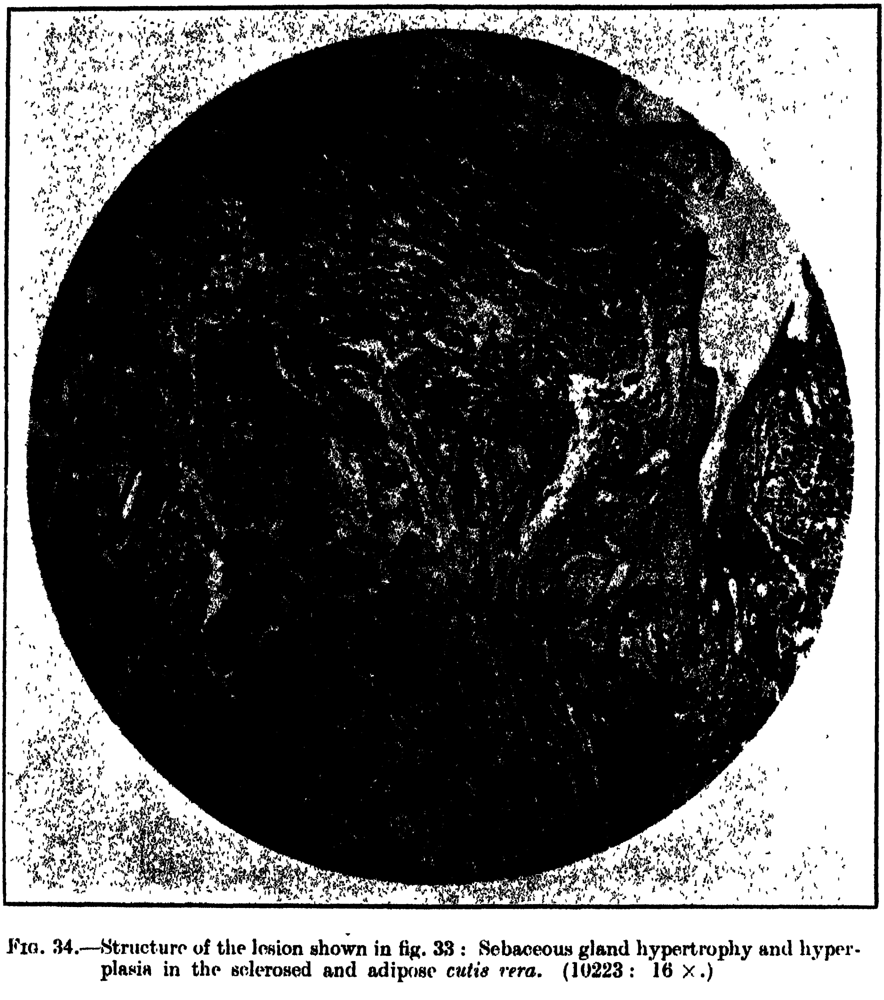

FIG. 34.—Structure of the lesion shown in fig. 33: Sebaceous gland hypertrophy and hyperplasia in the sclerosed and adipose *cutis vera*. (10223: 16 ×.)

together with the pressure of the densely collagenised surrounding connective tissue, is doubtless responsible for their frequent occlusion, reflected in the appearance of cysts lined by stratified epithelium and filled with fatty and keratinous debris. In one section such cysts reach a diameter of 3 mm., being readily visible to the naked eye. Further factors in this tumour-like thickening of the skin are: (*c*) a lipomatosis of the derma, wherein occur large and small collections of fat-cells extending vertically downwards into the subcutis. There are also actual free " pools " of fat lying in the connective tissue; and (*d*) a diffuse cellulation (lymphocytes and plasma cells) occurring especially in the vicinity of the glands. There are also definitely focal accumulations of such cells mixed with variable and even considerable numbers of neutrophiles and macrophages. Some of these foci are actually encapsulated, forming minute abscesses.

Deeply the tumour is not specially encapsulated from the subcutis, into which it passes by a thinning of the collagen bundles, by the continuation of the dermal adipose tissue into the same tissue of the subcutis, and by the limitation of the altered glands to the derma. The epidermis in parts shows hyperkeratosis.

Discussion.—This tumour must be unique in size for one derived from sebaceous glands. Sebaceous " adenomas " are not usually described as exceeding the size of a walnut. Tumours fundamentally identical with this one have often been termed sebaceous adenomas. While a true adenoma of sebaceous glands may perhaps exist, one must be cautious in applying this term indiscriminately. As Gans (1928) has pointed out, the distinction of adenoma from hypertrophy can scarcely be made, and he indeed considers it advisable to avoid the use of the term adenoma in connection with sebaceous glands: such lesions fall either under hypertrophies or under congenital naevi. The chief objections to applying the term adenoma in the present case would appear to be: (*a*) lack of encapsulation (a doubtful objection); (*b*) the diffuse dissemination of the affected alveoli, indicating more a hypertrophy of existing glands than a new formation from a single centre: what new growth there is, in other words, concerns rather the formation of new lobules from old glands than the formation of new gland-like units as a whole; (*c*) the presence of ducts. These last two objections appear to us to be very well taken, and in view of them we would hesitate to apply the term " adenoma " *in sensu stricto*.

The condition, in its pathology, appears to correspond closely in essentials with that lesion of man known as rhinophyma—a hyperplastic and inflammatory process affecting the nose, in which the derma shows fibrosis and the sebaceous glands hyperplasia (*vide* Gans, pp. 179 ff.). We are here dealing with a much more exaggerated form of such a pathological change, but there seems to be no special term applicable to a lesion corresponding histologically to rhinophyma but situated elsewhere than in the nose. Ewing (p. 500) remarks, under the subject of sebaceous adenoma, on a form of hypertrophy and hypersecretion " which may approach neoplastic grade ". He deals with the lesion in connection with those overgrowths of gland tissue " which should be separated from true adenoma, although no sharp line divides these conditions from true tumours, and, in many instances, the one passes into the other ".

My opinion of this lesion was that it is not a true neoplastic process: yet it reaches very gross dimensions actually unparalled by lesions of the same general kind which have a clearer claim to be considered neoplastic. For purposes of convenience this growth has been grouped in the collection with the neoplastic processes affecting sebaceous glands. Had there existed sebaceous " adenomas " which clearly fulfilled all Borst's criteria of adenoma (e.g. encapsulation, considerable differences from the normal in the finer structure of the glands, etc.), I should have hesitated to do this. But to the practical man this lesion is essentially a " sebaceous adenoma " and tentatively, pending comparison with true (?) sebaceous adenomas, if such should be met with, it has been grouped as such. No case resembling this has been found by me in the veterinary literature.

Diagnosis.—Sebaceous gland hypertrophy and hyperplasia reaching neoplastic dimensions (" *adenoma sebaceum* ").

Summary of the cases of Adenoid Epithelioma in Dogs.

The skin of aged dogs provides excellent material for the comparative study of cutaneous neoplasms, and although we have been able here(11) to do little more than to draw attention to the problems concerned, it is evident that much closer attention is demanded in order to elucidate the relationships of sebaceous neoplasia and hyperplasia on the one hand and the basal-cell carcinomas and acanthomas on the other. Pathologically the lesions we have studied have consisted in (1) sebaceous epithelioma arising from the perianal glands (the best known of these tumours and a type regarding which a considerable literature already exists); (2) sebaceous epitheliomas ot small size occurring as (*a*) multiple lesions, one of which apparently has progressed to frank sebaceous " carcinoma ", or (*b*) multiple lesions associated with basal-cell carcinoma, or (*c*) multiple lesions accompanying acanthoma. These small epitheliomata apparently represent early stages of malignant tumours and from them may probably develop frankly malignant (invasive and metastasizing) sebaceous epitheliomata (carcinomata) and possibly also basal-cell carcinoma and even acanthoma. Some of these small epitheliomata appear to arise as proliferations of (pre-existent) sebaceous glands, others from the walls of the hair-follicles, and still others as a new formation of " sebaceous glands " from the *stratum basale* of the epidermis. A study of a far greater number of these lesions (which I think are quite common) would be necessary to prove the truth of these suspicions; (3) hypertrophic-hyperplastic changes of pre-existent sebaceous glands accompanied by chronic dermatitis and local lipomatosis producing massive localised enlargement of the derma attaining neoplastic dimensions, but not considered a true neoplastic process.

Adenoid Epitheliomata in other Species.

Neoplasms classed as adenoid epitheliomas have been encountered, apart from among dogs, only in the Angora goat. A lesion of the skin of the external ear of a sheep (Ovine, 9041) had previously been diagnosed at this Institute as an adenoid epithelioma, but on re-examination it was classed as multiple epidermoid and retention cysts of the sweat-glands. It is mentioned here only from the standpoint of differential diagnosis. The lesions of Angora goats arising from sebaceous glands have been carefully described by Thomas (1929). Two of his published cases are in the histological collection. The one—

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(11) The study should be applied to a larger number of cases. They are probably of quite frequent occurrence, but the early stages are apparently usually dismissed as " warts " and are not submitted to pathological examination.

Case 5 (*Caprine*, 8507)

was correctly described by that author (pp. 723-4) as a " proliferation of sebaceous gland basal epithelium . . . with accompanying acanthosis". A prominent feature of the lesion is the *hyperkeratosis suprafolliculorum* (" fissures or cavities usually filled with keratin ") separating the acanthotic rete pegs of the epidermis. As I was in the case of the lesions of the dog, so was Thomas impressed by this lesion as " probably an early stage " of epithelioma and he further makes the interesting suggestion that from the acanthotic surface epithelium might arise acanthoma and from the " basal " epithelium of the sebaceous glands the lesions which he terms basal-cell epitheliomas: by this means the existence of his mixed spinous and " basal-cell " tumours would be aptly explained. I feel that great weight should be attached to this shrewd suspicion.

Diagnosis.—Adenoid (sebaceous) epithelioma associated with (pre-cancerous?) acanthosis. The lesion is almost certainly an early stage of malignancy.

The other lesion—

Case 6 (*Caprine*, 8481)

has been described also by Thomas (1929, pp. 692-3). Here, too, we have to deal with a proliferation of the sebaceous glands with imperfect differentiation of the cells. In this case, however, there is scarcely any accompanying acanthosis and no hyperkeratosis. The lesion is still circumscribed, but is rapidly proliferating and cannot be termed an adenoma.

Diagnosis.—Adenoid (sebaceous) epithelioma.

Remarks on the Sebaceous Epithelioma of the Goat.

I do not intend to add much to the very full discussion already to be found in the work of Thomas (*loc. cit.*). These sebaceous proliferative lesions were encountered by him in the Angora goats in which both acanthomas and pigmented epitheliomas are found to be so frequent, the second adenoid epithelioma actually having been obtained from a subject from which a " basocellular epithelioma " had previously been removed from the same region, viz., the perineum. Thomas strongly suspected that such epitheliomata were the immediate forerunners, indeed actually the early stages of malignant tumours: and from my own observations in dogs I feel that his suspicion was fully justified(¹²). There are two animals in

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(¹²) It is hoped to collaborate with Dr. Thomas in a further discussion of his caprine specimens.

which proliferations of sebaceous cells, apparently early stages of malignancy, are found with fair frequency—the dog and the goat. In the former, basal-cell carcinomas are common, scarcely occurring in any other domestic animal. They may occur actually together with basal-cell carcinoma in the same subject—a primary multiplicity. [But instead of being accompanied by a basal-cell tumour they may be associated with either acanthoma or fully malignant sebaceous epithelioma (sebaceous carcinoma).] In this species also, adenoid (sebaceous) epitheliomas of the perineal region (arising there from the perianal glands) are reported common. Compare with these facts the following, relating to the goat, in which subject sebaceous precancerous proliferation also appears to be common:— In this species, in addition to acanthoma, occurs a peculiar, highly malignant, and metastasizing epithelioma to which Thomas has applied the term basal-cell carcinoma. These tumours are, however, usually heavily pigmented. The tumours in question have as a favourite site the perineum. Those who favour the development of basal-cell carcinoma from sebaceous epithelium will doubtless welcome these facts. They are certainly most significant, but one would prefer to reserve at present one's judgment of the three questions: (1) the histogenesis of true basal-cell carcinoma; (2) the relation between the goat tumour which Thomas has called basal-cell carcinoma and (*a*) the true basal-cell tumours, e.g. of man and dog, and (*b*) previously known melanotic neoplasms; (3) the correct place in the classificatory scheme of non-acanthomatous epitheliomas of the goat (caprine melanocarcinoma, basocellular epithelioma of Thomas).

CHAPTER III.

Tumours of Epithelium (Contd.): Adenoma and Carcinoma.

Adenoma.

BENIGN tumours of glandular epithelium are not common in domesticated animals, if we except the thyroid adenomata (*strumae nodosae*) which are so often encountered in old horses. But a number of lesions are often termed adenomata which are better classified in a different manner. These lesions include so-called adenomas and "malignant adenomas" of the liver of oxen nearly all of which are really carcinomas, renal adenomata which are usually nothing

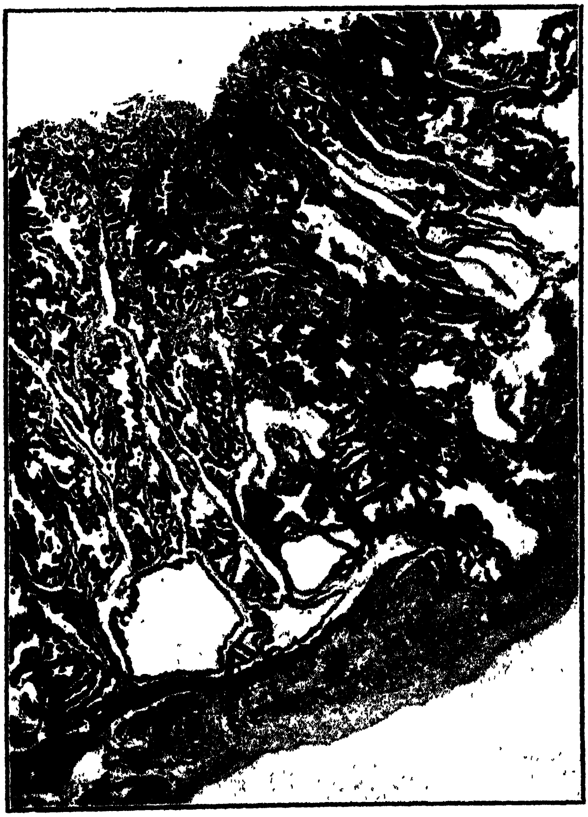

FIG. 35.—Adenomatoid hyperplasia of Brunner's glands in the small intestine of the sheep: Greatly thickened submucosa due to a diffuse and partly cystic glandular proliferation affecting the whole circumference of the bowel. (4333; 100 ×.)

but embryonal nephromas in which an adenomatoid type of growth predominates, "adenomas" of adrenal cortical tissue which should rather be termed benign hypernephromas (*qq.v.*), and "sebaceous adenomas" (which have been considered with the epitheliomas in the preceding chapter). In addition there are adenomatoid hyperplasias such as are found in the thyroid, liver, and intestine (Brünner's glands in the sheep—see Fig. 35) which not infrequently are unsuitably termed adenomas. Some of these lesions will be mentioned elsewhere.

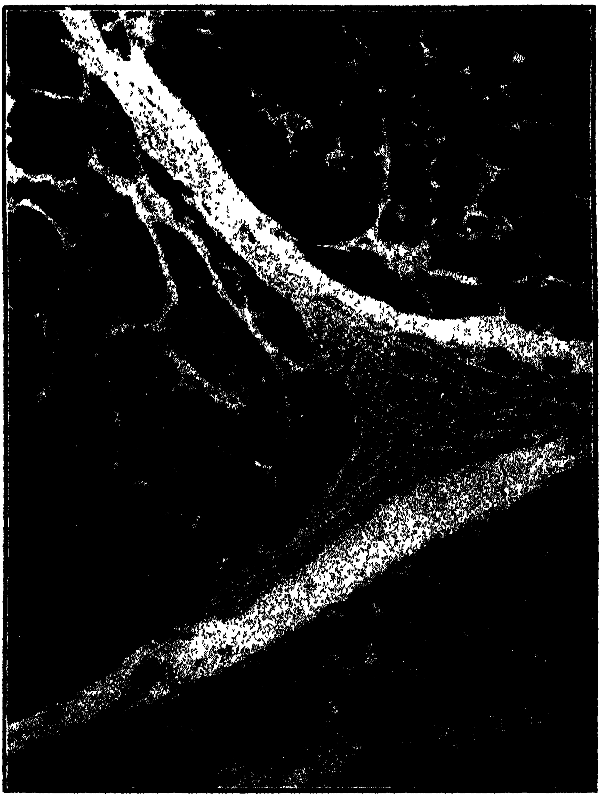

FIG. 36.—Structure of multiple adenoma of the pancreas in the bovine: Encapsulation against the normal pancreatic tissue (below); from centre to above runs a trabecula of the stroma separating two lobules of the neoplastic tissue consisting of acini of cells which do not differ from the normal except for their somewhat larger size. (2162; 240 ×.)

Of lesions, to which the application of the term adenoma is without serious objection, the Onderstepoort collection contains only 13 examples. Six of these are thyroid adenomas (*strumae nodosae*) of horses, two are hepatocellular adenomas associated with adenomatoid hyperplasia of the liver of pigs, and one is an hepatocellular adenoma of the liver of an ox. These are dealt with in Chapter IV. The remaining 4 cases comprise an example each of multiple adenoma of the pancreas—Fig. 36 (bovine, 2162), adenoma of the kidney [1] (bovine, 5634), adenoma of the testicle (benign "seminoma"—canine, 5826), and lastly an adenoma of the male breast—the only adenoma which it is necessary to report here in detail. Such tumours are considered rare in human pathology and I can find no record of their occurence in domestic mammals.

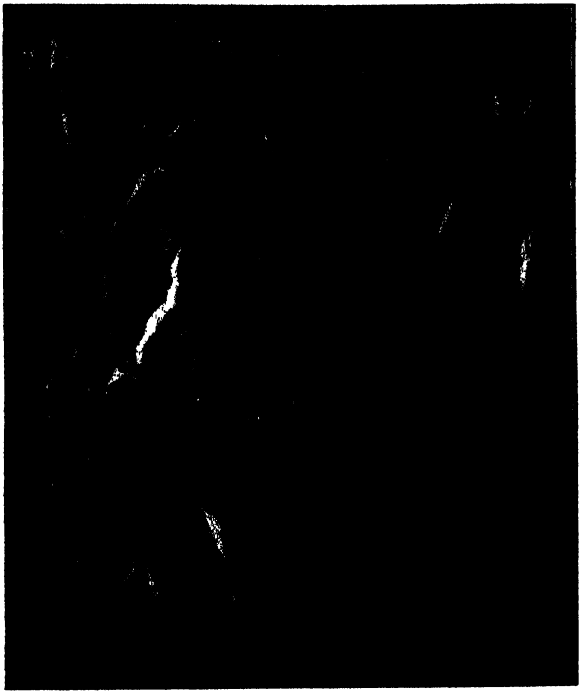

FIG. 37.—*Adenoma fibrosum* ("fibroadenoma") of the male breast in the dog. (16149 ; 70 ×).

(*Canine*, 16249.)

The tumour was situated in the abdominal wall of a male fox terrier, producing a prominent, ovoid or short-cylindrical protuberance beneath the tense and hairless skin. It was placed on the right side, 2 inches cranial to the penis and slightly lateral to the umbilicus, corresponding in position to the abdominal mamma; and indeed it was symmetrical with an abdominal nipple of the opposite side. It was removed by operation, being, on account of its good circumscription, easily dissected out, and there was no recurrence after 6 months. On section the specimen has a firm consistence and is pinkish white in colour. It measures 4 × 2·5 cm.

Microscopically (Fig. 37) the tumour is not specially encapsulated but is well demarcated from the overlying *cutis vera*. It consists of a rich and in many parts quite cellular connective-tissue

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(1) This lesion could not be classed with the embryonal nephromata because only the adenomatous moiety was demonstrable. One feels, however, that such tumours may represent extreme one-sided development of embryonal nephroma, characterised by a slow and benign type of growth.

stroma in which are embedded, at intervals, slightly branched and usually narrow tubules lined by epithelial cells. The latter are somewhat variable; in most cases they are very tall (e.g. 45μ) columnar elements arranged in a single layer and with well-preserved polarity. Their elongate-oval nuclei are situated towards the distal pole of the cell. In such cases the lumen is a narrow slit. One can also usually speak of the presence of a basement membrane. Less often the epithelials are cuboidal or even flattened and the lumina correspondingly more prominent. Sometimes there is thickening of the acinar walls into several layers of cells which may be more irregularly arranged, and small, almost solid alveoli of cells bordered by no distinct basement membrane may thus arise. The nucleoli are usually single and distinct, the n : N ratio reaching *ca.* 1 : 14. The lumina contain a somewhat granular eosinophilic material with a few desquamated cells. Mitoses are fairly frequent.

Remarks.—Histologically this tumour corresponds to the *fibroadenoma pericanaliculare* of human pathology. Schultz-Brauns (1933) includes such tumours under simple neoplasms (*adenoma fibrosum* or "*Adenom vom Bau der ruhenden Brustdrüse*") (2). One of such tumours is Ewing's foetal fibroadenoma, with which this neoplasm seems to have most in common. The embryonal character of the tumour cells in this case is impressive; one cannot, however, demonstrate transitions to fibroblast-like cells as in the case of many other (mixed) neoplasms of the dog's breast or in embryonal nephromas. It is interesting that in man tumours of the male breast also usually possess this structure.

Diagnosis.—Adenoma fibrosum of the male breast, probably an embryonal tumour ("foetal fibroadenoma").

Carcinoma.

Under this category we include malignant epitheliomas, which have been discussed earlier, and the malignant tumours of epithelial cells of other types. In arranging the Onderstepoort collection the number of cases to be included in this diagnosis was greatly reduced by the elimination of the following tumours from this heading: thymoma ("thymic carcinoma"), mesothelioma (primary "carcinoma" of serous membranes), and mixed tumours (such as those frequently occurring in the breast of the dog and the embryonal nephromas) which possess a carcinomatous moiety. It is consequently not possible to compare with accuracy our figures for carcinoma with those given by many authors whose conception of what should be included under carcinoma does not depend on strict histological or histogenetic definitions. Under the carcinomas we have included also the tumours commonly termed adenocarcinomas and for the following reasons:—

The term adenocarcinoma is a most unfortunate one, since the compound names of oncological nomenclature have been and should be reserved to denote mixed tumours. That the use of such a term to describe also a simple tumour may confuse not only the elementary student but also the qualified pathologist is evident from the statement frequently encountered in textbooks that adenocarcinoma is a mixture of adenoma and carcinoma (thus is put on a par with, for example, a tumour like leiomyoadenoma). The keynote of the definition of both adenoma and carcinoma being their respective benign and malignant behaviour, it is manifestly absurd to postulate the possibility of a mixture: it amounts, in effect, to the pathologist's answering, when asked the question, "Is this epithelial tumour benign or malignant?", that it is both. I need not labour further the need that what many attempt to describe as adenocarcinoma, should far more properly be termed, with Borst, adenoid carcinoma, or with v. Hansemann (1910), "*Krebs geringer Anaplasie*". Both these terms, especially the latter, express with great clarity the idea that the term adenocarcinoma attempts to convey, viz. a carcinoma, a malignant tumour, characterised histologically by a limited departure from the normal structure, in other words, by a marked resemblance to adenoid tissue, or, still more concisely, by limited anaplasia.

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(2) In contradistinction to *A. purum* or "Adenom vom Bau der sezernierenden Brustdrüse".

Secondly, I have found it quite impossible to carry out an intelligent histological classification of malignant epithelial tumours of domestic animals if adenoid and other carcinomas are to be kept in separate categories. Not only is it apparent that, among different tumours, between "*geringe Anaplasie*" and "*sterkste Anaplasie*" all intergrades (*vide* v. Hansemann's "*sterkere Anaplasie*") exist: but, further, in one and the same tumour may be found frequent transitions from an adenoid to a frankly anaplastic type of growth. This is excellently illustrated by glandular carcinomas in the fowl, in which, as Pentimalli (1916) has described, all transitions between the arrangements commonly described as scirrhous, medullary, and adeno-carcinoma may be found in (the metastases of) one and the same tumour. I am aware that I go against the majority of English authors in this attitude, yet "adenocarcinoma" is always discussed in texts under carcinoma; it is not the conception implied by the use of the term that I object to, but simply the construction of the term itself.

Occurrence.—The Onderstepoort collection contains 217 malignant tumours of epithelium (carcinomas) of which 104 epitheliomas have already been dealt with and of which 21 belong to the melanotic epitheliomas mentioned in Chapter VIII. The remaining 92 neoplasms are carcinomas in the narrow sense and are distributed among the species as follows:—Equines, 5; bovines, 22; ovines, 11; canines, 7; poultry 45; species unknown, 2.

These figures will at first seem surprising on account of the relative frequency of carcinoma (in the narrower sense) in oxen and sheep as compared with the dog. Carcinoma, apart from epithelioma of the skin, is considered a rare disease in sheep, and it is most unusual for a single observer to encounter as many as 11 cases. The low figure for carcinoma of the dog is doubtless mainly referable to my having relegated all the malignant tumours of the mammary gland in this species to the category of mixed neoplasms, since in all cases a mesodermal or sarcomatous moiety was demonstrable in addition to the epithelial. The high incidence of carcinoma in the domestic fowl is well known: it is second in frequency only to lymphocytoma (lymphoid leucosis). Poultry show an overwhelming preponderance of (glandular) carcinomas over epitheliomas, which constitute only about 6 per cent. of the malignant epithelial tumours; in contrast with the domestic mammals in this country, for which the corresponding ratio is 78 per cent. Carcinomas of the domestic fowl will therefore be considered first on account of their importance.

CARCINOMA IN POULTRY.

In poultry, 45 glandular carcinomas were encountered, including one case in a turkey. Of those cases in which the site of the primary tumours was known, the great majority (21) affected the female reproductive tract (ovary or oviduct), while only 3 cases of carcinoma of other organs were found. In a very large proportion of cases only secondary lesions (almost always peritoneal implantations) were submitted for examination and it is doubtless correct to assume that in all these the primary tumour was situated in the reproductive organs. The only carcinomas, apart from those of the ovary and oviduct, were one case each in the pharynx, the liver, and the intestine. The liver carcinoma (*C. hepatocellulare*) is described in Chapter IV. The pharyngeal carcinoma (*C. leiomyomatosum*) is more conveniently referred to after a discussion of leiomyomatose carcinomas of the fowl in general.

(1) *Carcinoma of the Intestine.*

A considerable misconception exists regarding the frequency and importance of this lesion in the fowl. It is true that there are authentic reports of the disease in question—Ehrenreich and Michaelis (1906), Ehrenreich (1907), Petit and Germain (1909), Joest and Ernesti (1916)—and it is probable indeed that primary carcinoma of the bowel is more frequent in fowls than in domestic mammals, in which this disease may be considered rare. But there have been many reports—and even some of the textbooks are guilty of this error—of cases of " carcinoma of the intestine " which were nothing more than transcoelomic implantations on the mesentery and bowel-serosa from a primary tumour elsewhere. It is surprising that even so great an authority as Feldman (1932) has apparently been uncritical in regard to this question, making the statement (on p. 312 of his work) that " adenocarcinoma of the intestine is common " and referring to his Fig. 148 as an example. The illustration in question, labelled " adenocarcinoma of the mesentery of a chicken " is as typical a case of secondary peritoneal carcinosis as one could wish to see, there being not the slightest indication of a primary involvement of the bowel; one could safely predict that a microscopic examination of the specimen photographed would show little if any extension into the bowel beyond the subserosa and that the tumour nodules would nowhere reach anywhere near the intestinal mucosa. I cannot believe that Feldman really regards this as a primary tumour of the intestine, yet it is equally hard to credit so meticulous a worker with the looseness of nomenclature which the alternative implies. Consequently Feldman's figures for the organ distribution of carcinoma in birds investigated by him are misleading: he found no fewer than 6 out of 15 carcinomas of the chicken to be of the type referred to, and only 5 cases affecting the female reproductive tract.

On the other hand, it appears that only the case in which "an adenocarcinoma of the mucosa of the ileo-cecal juncture . . . occupied about half the circumference of the lumen. Metastasis had not occurred " is worthy of consideration as a primary intestinal tumour. Feldman's figures would thus read: carcinoma of the female genital tract, 5 cases; secondary peritoneal carcinosis (in most, if not all, cases secondary to a primary of the genital organs), 5 cases; carcinoma of the intestine, 1 case; thus agreeing closely with what we ourselves have found to be the case. It is evident then, that a satisfactory report of primary carcinoma of the avian bowel should fulfil at least one of the following criteria:—(*a*) Genital tract negative, after minute scrutiny at autopsy; (*b*) demonstration of actual continuity with intestinal epithelium, or that the tumour affects essentially the mucosa with extension into muscularis, not the serosa with extension into muscularis; (*c*) a solitary lesion of the bowel without (other) metastases; or if metastases present, clearly of a " younger

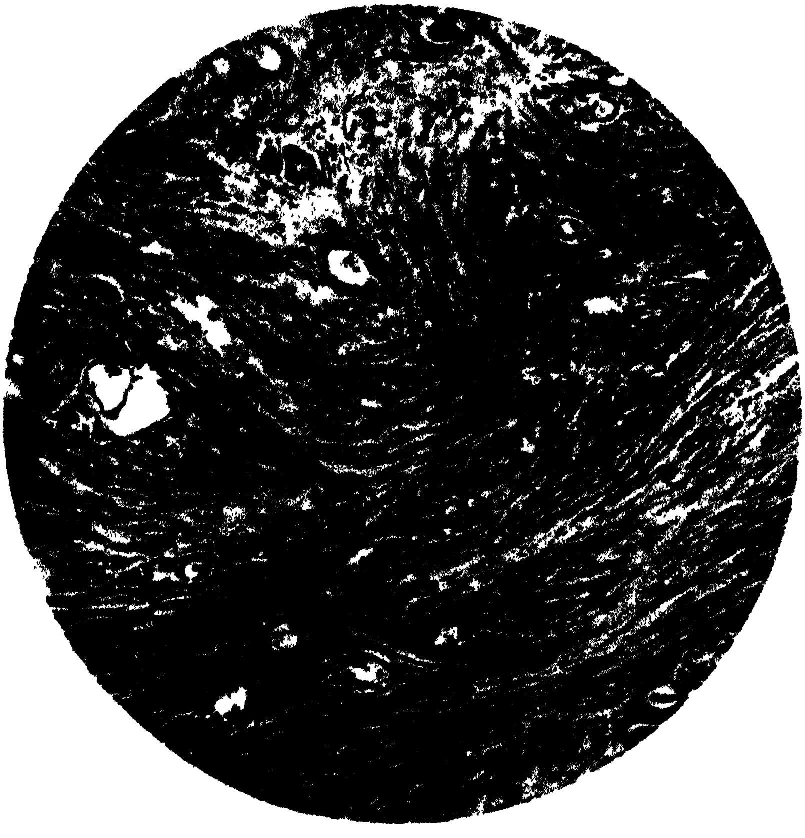

FIG. 38.—Structure of primary carcinoma of the intestine of the fowl: A stenosing tumour with scirrhous type of growth. (14952; 110 ×.)

generation " ([3]) than the tumour considered as primary. In a word, secondary serosal carcinosis of the bowel is so very frequent in birds that there is an onus on anyone reporting a primary lesion adequately to exclude this possibility and not merely to disregard it, as is so often done.

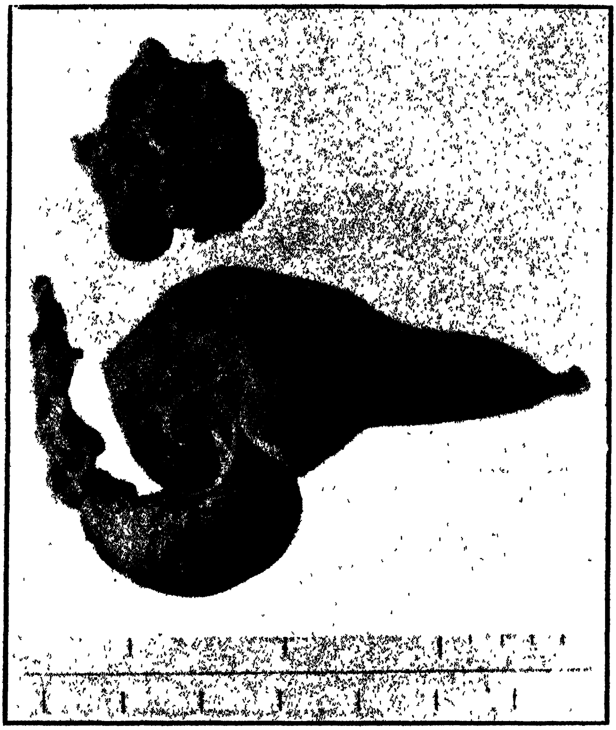

FIG. 39.—Intestinal stenosis in the fowl produced by an implantation tumour situated about an inch posterior to the pylorus: The point of stenosis is seen at the left of the lower figure: cranial to this are the greatly dilated bowel, gizzard, and glandular stomach (right). Above, the primary tumour (Carcinoma leiomyomatosum) affects the ovary. (15814; 2.5 ×.) Scale in inches (above) and centimetres (below).

True primary carcinoma of the bowel of the fowl is usually an ulcerating, stenosing tumour, often growing in scirrhous form (Fig. 38) and although it may penetrate the serosa, and give rise to secondary peritoneal implantations, it usually (and earlier) causes true (blood-borne) secondaries in the liver; while secondary implantations of carcinoma on the bowel serosa are in their earliest stages confined to the subserosa, where they are multiple and numerous. Later they penetrate the muscularis. They seldom progress further than to the outer aspect of the inner (circular) layer of the muscularis. Occasionally, however, that layer may to some extent be invaded. Rarely there is complete penetration of both

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([3]) By this I am attempting to indicate that the metastases should be smaller in size, essentially lesions of the serosa, and not ulcerating, stenosing lesions of mucosa and muscularis.

muscular coats, but I have never seen invasion of the mucosa, although I have observed a commencing penetration of the submucosa. A solitary, penetrating transcoelomic bowel implantation (Fig. 39) must on no account be confused with a primary of the bowel. Thus there are definite criteria to be applied in distinguishing between primary and secondary carcinoma of the bowel and the confusion would appear to be due largely to a mere looseness in the application of nomenclature.

(2) *Carcinoma of the Female Genitalia.*

Of 21 primary carcinomas of the female genital organs 17 were primary in the ovary and 4 were primary in the oviduct. Included with these cases are 4 cases of *carcinoma leiomyomatosum* of the oviduct or ovary—tumours which behave identically with the pure carcinomas, but which some would group under the mixed neoplasms. Their histology is identical with that of the carcinomas, save that where in pure carcinoma one expects to find a connective-tissue stroma, this is largely or even completely replaced by smooth muscle in the tumours in question. The dilemma confronting one when wishing to classify these tumours is further referred to in connection with the mixed tumours, where the growths in question are discussed.

The pathology and histopathology of ovarian and oviducal carcinoma of the fowl are well known and we do not here intend to give a detailed description of the lesions. Suffice it to say that ovarian carcinoma occurs usually as a much lobulated growth, in conformity with the lobular structure of the organ that it infiltrates; and oviducal carcinoma as an ulcerating, stenosing growth originating from the mucosa, infiltrating the muscular walls, and finally penetrating the serosa. The growths may appear identical in histopathology from whichever organ they originate and further they agree in giving rise early to multiple and often very widespread transcoelomic implantations and in having little or no tendency to form true metastases, which I have never observed in this disease, although Petit (*cit.* Joest) reported hepatic and renal metastases from primary carcinoma of the oviduct. Histologically, we have found that both types of tumours consist, as Joest has indicated for the ovarian tumours, "*aus Drüsenschläuchen mit krebsischem Epithel und engem Lumen, das auch met Epthel vollständig gefüllt sein kann, oder aber das Blastomparenchym setz sich aus zahlreichen, soliden Epithelzellnestern zusammen, oder Schläuche und Nester wechseln miteinander ab. Das bindegewebige Statzgerüst durchzieht die Geschwulst in Bändern und Streifen und kann eosinophile Leukozyten enthalten*".

What Joest does not mention, and what appears to have escaped notice (4), is that in a considerable proportion (4 out of 21 cases of primary epithelial tumours of the genital tract) this connective-tissue stroma is entirely or completely substituted by smooth muscle tissue. I have devoted considerable thought to the question of whether such tumours should be grouped with the mixed neoplasms or not, and while it seems that there are weighty arguments both in favour of following that procedure and in favour of not doing so, it is advisable for practical purposes to discuss the tumours in question along with the pure carcinomas. The problem is dealt with again under the discussion of mixed neoplasms, but I may here mention the considerations which have received attention in this connection:—

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(4) Joest and Ernesti (1916) have however reported two cases of "adenomyoma", one affecting the bowel and considered primary, the other being multiple lesions of the oviduct. These tumours had not been previously reported and the authors did not take into account the possibility that they might have been secondary.

1. There is considerable variance of opinion regarding the extent to which the stroma (using that term in its widest sense) of a tumour should have to be developed before the term " mixed " is applied to the tumour tissue. The difficulty occurs, for example, with papillomas, which by some are considered to be mixed tumours (fibro-epitheliomas) especially when the connective tissue " stroma " is strongly developed. It is quite customary to label many tumours of the uterus leiomyofibromas on account of the prominence of the collagenous connective tissue. Yet a satisfactory case for the conception that the fibrous moiety, as well as the adenomatous or the leiomyomatous moiety, is neoplastic is often not made out. Others (e.g. Borst) tend rather to regard the development of fibrous tissue as a secondary process called up by the presence of the growing " parenchymatous " moiety and consider it as nothing more than an excessively developed stroma; such an attitude is indicated by the use of the terms *adenoma fibroides, leiomyoma fibrosum*, etc.; and to distinguish such tumours from genuine mixed tumours such terminology is most useful and simplifies the subject considerably.

2. Accepting for the moment that this conception is correct, should we not deal in the same way with the " stromal " or supporting moiety of a tumour, whatever the nature of that moiety may be? If, in other words, a tumour whose supporting moiety is excessively developed and is of the nature of connective tissue is to be described by the qualifying term " fibrosum " and not as a mixed tumour, should we not do exactly the same with a tumour whose supporting moiety is not connective tissue but smooth muscle tissue? If we hear the objection that smooth muscle tissue is not even suitably to be described by the term stroma, we point in refutation to an organ such as the ovary, in which the tissue which exercises exactly the same supporting function as is usually performed by connective tissue is well known to be by no means of connective tissue nature, but rather of smooth muscle type, or at least of a mixture of or transition between the two. Yet here we would not hesitate to speak of the tissue in question as a stroma for the epithelial elements. This objection would not, then, appear to be a serious one.

3. It is worth attention that it is in the tumours of the very organ (ovary) which has been used to illustrate this argument and whose stroma is of the peculiar nature mentioned that smooth muscle tissue comes to constitute such a prominent feature, in other words, reflecting the normal histology of the organ. The phenomenon is however not confined to the ovary itself but is also seen in tumours of the oviduct and oviducal ligament in avians and in tumours of the uterus and broad ligament of mammals. Thus in both ovary and

oviduct of the bird we find tumours of epithelium supported by smooth muscle (leiomyocarcinoma, or adopting the nomenclature suggested, *adenocarcinoma leimyomatosum*); while pure leiomyomas (as well as *leiomyoma haemangiomatosum*) occur frequently in the oviduct and oviducal ligament and *leiomyoma fibrosum* (Fig. 152) occurs in the ovary; and in the mammal the occurence of " myofibroma " (i.e. *leiomyoma fibromatosum*—the common " fibroid ") is equally well known in the uterus and broad ligament. It thus appears that the female reproductive organs, whether avian or mammalian, are considerably predisposed to the proliferation of smooth muscle, whether as a simple tumour, whether as one moiety of a mixed tumour, or whether as a stroma-like element of what are more practicably to be regarded as simple tumours. The rôle of the normal smooth muscle element in the ovary, however, still remains much of a mystery in histology, there being no final agreement as to the exact nature of the ovarian stroma: whether a mixture of plain muscle and fibrocytes, whether cells actually intermediate between plain muscle cells and fibrocytes are concerned, or whether we are to regard the elements in question as modified fibrocytes or modified smooth muscle cells. In this uncertain state of our attitude it is obviously unwise to come to any hasty conclusions regarding the further problems which confront us in the neoplastic. It seems likely, however, that the problems of both the normal and the neoplastic, outlined above, are closely linked; and that the histologist who is interested in the nature of the ovarian stroma could profitably extend his observations to the neoplastic, where he will encounter not dissimilar difficulties in an exaggerated form.

4. Whichever attitude we adopt regarding the simple or mixed nature of the myo-epithelial neoplasms of the fowl, difficulties are encountered in carrying through our classification consistently. Thus, if we decide to name those tumours in which the epithelium is dispersed in a very large amount of smooth muscle (which has just as neoplastic an appearance as the same tissue in the pure leiomyomas of the bird) we are at once confronted with the dilemma of a graded series of tumours in which the smooth muscular moiety gradually diminishes, until finally it becomes unrecognisable except by the employment of special fibrillar stains; and in which its presence would undoubtedly be overlooked on ordinary histological examination by the unsuspicious. And I have, indeed, little doubt that in many of the reported cases of reproductive tract " adenocarcinoma " of the bird, this muscular moiety has been present but has not been noticed by the observers. If, on the other hand, we boldly call such tumours *carcinoma leiomyomatosum*, we have to face an equally serious difficulty presented by the gradation (Fig. 44) to tumours in which, now, the epithelial moiety becomes more and more inconspicious, so that, for example in (implantation) secondaries, it may actually not be possible to demonstrate its presence (Fig. 45): How can we call such a tumour " *carcinoma* "? How, indeed, call such a secondary anything but " leiomyoma ", the purely histological definition of which it completely fulfills?

5. Most important in this consideration is the observation that the mechanism of transcoelomic metastasis of tumours of the avian genitalia, whether the pure carcinomas or the leiomyomatous

carcinomas are concerned, is constant; i.e. in both cases it appears that the seeds responsible for the appearance of secondaries are epithelial cells alone. This means, in respect of the "mixed" variety of tumours, that the proliferation of smooth muscle is a secondary effect set up by the presence of the epithelial cells wherever they happen to fall on a spot where pre-existing smooth muscle is available. It is most fortunate that we have been able to show that this is the case, and our evidence, which we think may claim to be regarded as satisfactory, has a three-fold basis:—

(i) demonstration that in the earliest metastases smooth muscle proliferation has not yet started;

(ii) demonstration of continuity between the proliferating stromal (myomatous) moiety and pre-existing muscle;

(iii) observation that in sites where smooth muscle is absent or not readily available the myomatous moiety fails to appear; the secondaries, e.g. in the liver and in the mesentery, growing as pure carcinoma with ordinary fibrous stroma.

It is this demonstration of the essentially secondary nature of the muscular moiety which prompts us to declare in favour of regarding the tumours in question as related to simple neoplasms rather than to mixed neoplasms and to employ for them the term *carcinoma leiomyosum* or *C. leiomyomatosum*. In arriving at this conclusion we have also been influenced by the fact that ovarian epithelium normally requires a peculiar stroma for its support, which has much of the myoid in its nature, and it is possible that the appearance of a muscular moiety for the support of neoplastic epithelium of genital derivation is naturally related to this phenomenon. The difficulty still remains of dealing nomenclaturally with lesions in which the muscle element greatly preponderates over the epithelial (Fig. 44) and with secondaries in which the epithelial moiety may actually be undemonstrable, apparently owing to regression (Fig. 45). The first difficulty need not be considered serious, and the term *carcinoma leiomyomatosum* is applicable to such lesions, on exactly the same basis whereon a carcinoma in which excessive development of the stroma renders the tumour alveoli inconspicuous is termed a scirrhous carcinoma (*carcinoma fibrosum*). In the second case, it epithelium is actually absent, the difficulty is perhaps a more serious, although probably a more academic one. Yet a scirrhous tumour in which the stroma had "strangulated" the tumour cells would still be called a carcinoma and only mistakenly (I presume) a fibroma. It may, however, be urged that a tumour arising from and consisting of plain muscle must be called a leiomyoma, even though its development was due to proliferation of muscle cells to provide a stroma for neoplastic epithelium which has been derived from an existing primary tumour. Be that as it may, the term leiomyoma for such a secondary would be utterly misleading and only the term "secondary *carcinoma leiomyomatosum* (with complete regression of the epithelial moiety)" could give an accurate representation of the pathology and pathogenesis of the lesion. And it may be noted in conclusion, as will be seen from the protocols, that this process of "strangulation" of the carcinomatous elements appears often to be most effectively achieved by the smooth muscle, which is probably to be regarded as having an equal, if not indeed a considerably greater facility in this direction than has connective tissue.

A second problem, which is even more interesting than that just discussed, has arisen in the study of the material in the Onderstepoort collection. It involves the vexed questions of: *(a)* What constitutes continuity as opposed to a mere invasive approximation (contiguity) of neoplastic and normal tissue? *(b)* What deductions regarding histogenesis may be inferred from the fact of continuity of a neoplastic with a "normal" tissue? and *(c)* the possibility of growth of cancer "by conversion". I may now describe a case which directly illustrates these fundamental problems and which at the same time serves to make us familiar with those genital tract carcinomas of the bird which are characterised by the leiomyomatous nature of their stroma:—

(Fowl, 15018.)

The subject was a White Leghorn hen aged 2 years and 8 months which had been under observation by my colleague Mr. D. Coles(⁵) for a period of 8 months. The history is that in August, 1933, abdominal malignancy was suspected on account of ascites. In September, at exploratory laporotomy, numerous implantation tumours were observed on the intestinal serosa. The peritoneal cavity having been evacuated of the ascitic fluid and the bird having recovered uneventfully from the operation, it was submitted to an experimental treatment for cancer which need not concern us here. Subsequently there was recurrence of the ascites, and on two further occasions the abdomen was drained of some 500 cc. of fluid. The last tapping was performed on 4th November, 1933. Afterwards the bird remained in apparently good health until about April, 1934, when the abdomen again became enlarged. On 7th May, 1934, the bird was seen by me and was of lively habitus, although the condition was poor and the "keel" prominent. The abdomen was moderately enlarged and fluctuating. On exploratory laparotomy (again performed by Mr. Coles), several hundred cc. of clear yellowish fluid were drained. On attempting to bring the bowels into view through the incision, this was found to be impossible, their coils being firmly adherent one to another and resisting all reasonable efforts at separation by traction. The only thing that could be withdrawn from the abdomen besides the fluid was a large yolk concrement lying free in the peritoneal cavity. The bird was there upon destroyed and the relevant viscera handed to me for autopsy examination:—

Macroscopically, the intestines are closely matted together by a conspicuous diffuse thickening of the mesentery, which in some places reaches a thickness of 4 mm. Especially the caeca and that portion of the ileum lying between them are affected, and are encased in a common mass of thickened visceral serosa, appearing externally as a single solid sausage-shaped structure in which the three lumina are detected only on cross section (Fig. 40). This thickening is of the nature of a pinkish-white, firm, elastic tissue in which small centres

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(⁵) Who generously gave me permission and all facilities to undertake an investigation of the pathology.

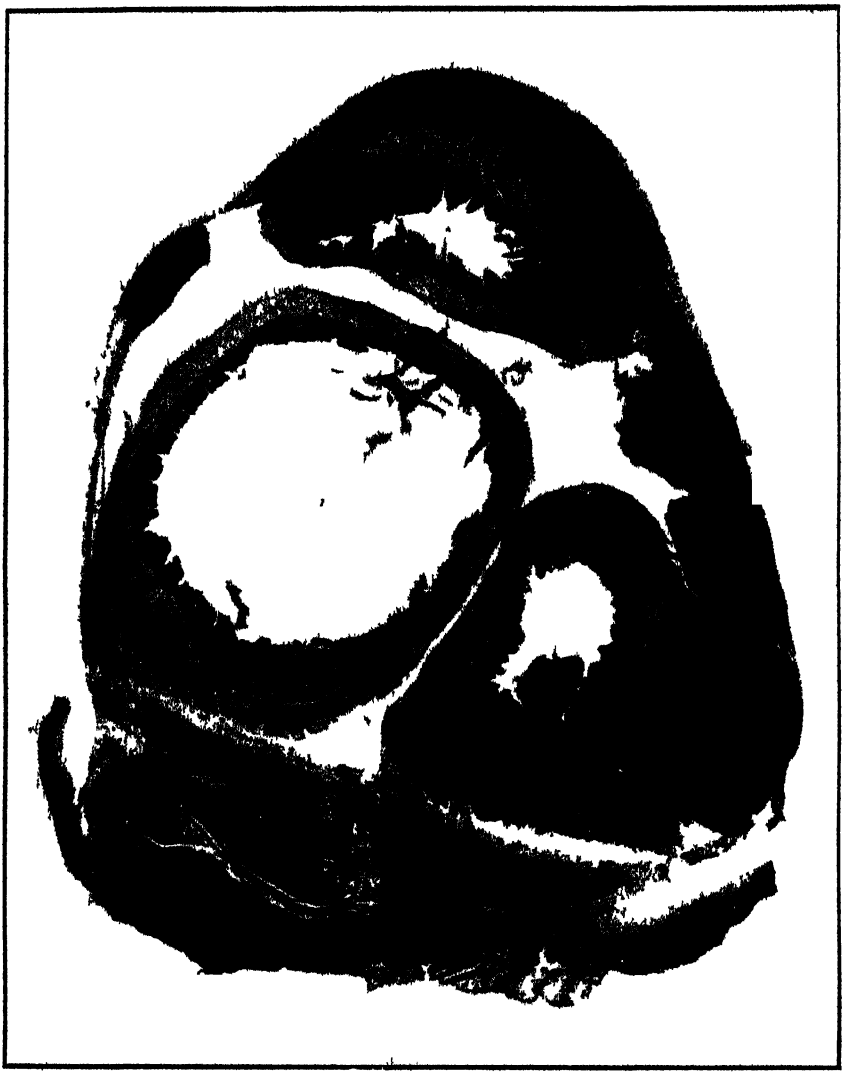

FIG 40.—Massive and diffuse thickening of the walls of the small intestine and caeca from a transcoelomic implantation of carcinoma leiomyomatosum (primary in the oviduct) of a hen. (15018, 5.5 ×.)

of a whiter colour can be seen. The surface here bears a number of prominent fibrous tags forming a fringe on the serosa; and in many parts the serosa, instead of being glistening, has a dull, opaque, yellowish appearance, somewhat resembling a mucous membrane. The rest of the bowel shows multiple, scattered, whitish foci situated subserously, causing elevations of the serosa and appearing to infiltrate to a variable extent the wall of the organ, although never (to the naked eye) so far as the mucosa. These are somewhat ill-defined and are often merged into more diffuse thickenings of the serosa; on section they also are seen to contain small and sharply delimited white specks. The ovary, especially to the one side, shows a partial replacement of its substance by firmer, whitish, neoplastic tissue which binds the ova together into a mass of firm consistence. The largest tumour occurs in the wall of the oviduct, forming a mass the size of a walnut (*ca.* 2·5 cm. in diameter); and in this region the ligament of the oviduct also is diffusely thickened, as well as bearing multiple discrete nodules which extend into the ovary to form the alterations there described. The liver is of a lighter yellow colour than normal and is friable; innumerable pin-point to pin-head sized yellowish-white foci are present; they are not confined to the capsular region, where they form small, flattened, circular elevations of the serosa and extend a short distance into the underlying parenchyma, but also occur throughout the substance of the organ, where they are, however, less prominent because they differ so slightly in colour from the rest of the liver tissue. Two of the liver foci are of larger size, one being oval and measuring 3 by 2 mm. the other spherical, 4 mm. in diameter, situated superficially, but extending into the deeper liver tissue and 'well circumscribed, although unencapsulated. The remaining organs show no significant change.

Microscopically.—The oviduct is sectioned at the caudal portion of the funnel region (transition to albumen-secreting portion) where tubular glands lie not closely packed in the *tunica propria*. In these glands mitotic cells are frequent (i.e. about 1 per field giving a view of some 8 transections of the acini). The neoplastic tissue (Fig. 41) is seen to grow diffusely in the wall of the oviduct, infiltrating as far inwards as the inner connective-tissue layer, and in most parts it does not invade the mucosa. It consists of a prominent " stroma " which is composed predominantly of smooth muscle cells arranged in broad strands and continuous with both layers of the muscular coat of the duct. In many places the stroma consists solely of such muscle tissue, while in other parts there is a variable admixture of collagenous connective tissue. This irregular, anastomosing system of muscular bundles, which in many parts actually dominates the whole picture, encloses epithelial cell-islands which are extremely variable in size and which are divided into units (appearing as branching tubules) by a system of fine to coarse secondary trabeculae composed usually of connective tissue but in parts consisting of finer bundles of smooth muscle fibres. The tubules have narrow lumina, often almost obliterated by the lining cells; the latter are of glandular epithelial type, having basal (proximal), ovoid nuclei and a large amount of cytoplasm packed with brightly refractile acidophilic granules (shown up still better by the van Gieson stain, with which they

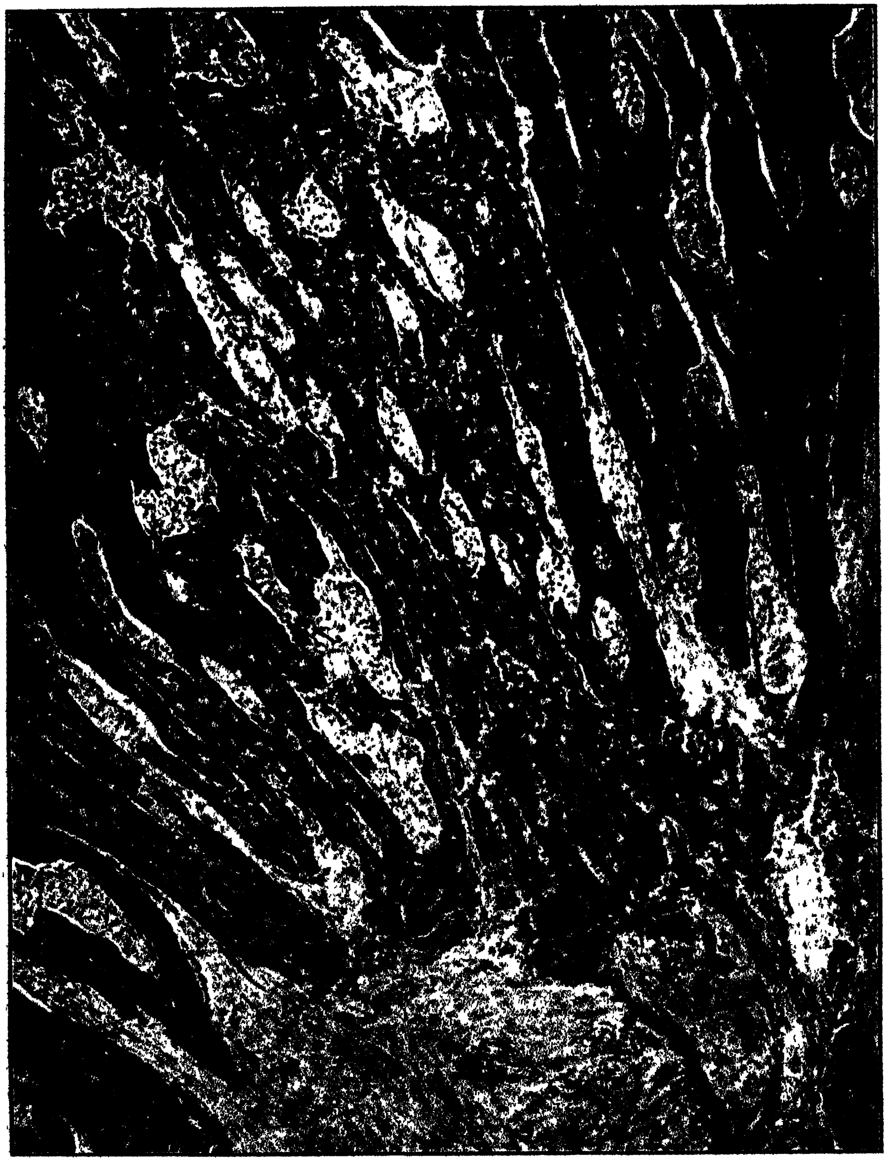

FIG. 41.—Carcinoma leiomyomatosum of the oviduct of a hen (same subject as fig. 40): The epithelial moiety is seen to become associated with a progressive increase of the muscular stroma as it grows outward from the mucosa through the muscularis of the duct. (15018; 140 ×.)

assume a bright yellow colour). The lumina contain a similarly staining hyaline secretion which may compress the lining cells from a columnar to a cuboidal or even flattened form. The granules can be seen in the process of discharge to join the free secretion. In parts, lumina and secretory granules fail, or are less in evidence, and more solid strands of epithelium are formed. Mitoses are (as compared with the non-neoplastic glands of the mucosa) more frequent, 1 to 2 per field, and in parts as many as 6 to 7 were counted. There is but moderate variation in nuclear size. There are usually two (but often three or only one) nucleoli which, relatively to the nuclei (themselves two to three times the size of the nuclei of the normal glands of the propria) are not enlarged. Many nuclei show hyperchromatosis. In transverse sections of the oviduct, the neoplasm has a crescentic outline, growing intramurally; between the horns of the crescent about one-fourth of the circumference of the duct remains uninvaded. The secretory granulation is in all respects identical with that of the non-neoplastic glands of the *propria mucosae*. The muscular stroma can be distinguished *cytologically* from the normal muscle by a slightly greater nuclear size, absence of slight irregularities (wrinkling) of the nuclear membrane (giving a plumper appearance to the nuclei) and still more by the greater prominence of the nucleoli. Sections from other parts of the oviduct show small tumour nodules localised to the subserosa and in which the epithelium shows greater anaplasia. Some of these tumours pass between the walls of the bowel and the oviduct, binding the two tubes closely together.

Sections of the ovary show the presence of a diffuse neoplastic growth, branching from lobule to lobule of the organ to form pedunculated, rounded masses usually limited by the serosa but not otherwise encapsulated, growing round the Graafian follicles without invading them, but breaking through the lymphatic endothelium (as papillary protrusions) so that free neoplastic cells are to be found in the lumina of the lymph-vessels. Further, the lymphatic endothelium itself is often seen to proliferate as elongated papillary projections into the lumina (collateral hyperplasia). In one section, penetration of the serosa was observed. The stroma is smaller in amount than in the oviducal tumour, but is here again a mixture of smooth-muscle-like elements and connective tissue, and is continuous with the ovarian stroma. In places, indeed, it appears that a specialised stroma is lacking, the epithelial cells growing in the normal (?) ovarian stroma without other support. Anaplastic changes in the neoplastic epithelium are here more marked than in the case of the tumour of the oviduct. The epithelium however is still arranged in tubules and has secretory function; but polarity of the cells is less well preserved, there being islands of cells lying in various directions, sometimes arranged concentrically. There is greater variation in nuclear size, some nuclei being twice the average size, and hyperchromatosis is pronounced. In many places there is not only absence of a basement membrane, but the whole boundary between epithelial alveolus and cellular stroma is exceedingly vague, especially since elongated epithelials occur with spindle- or cigar-shaped nuclei which can only be distinguished from the contiguous muscle cells of the stroma by the detailed structure of the nuclei (chromatin pattern, nucleoli). The n : N ratio of most of the cells appears definitely increased, e.g. 1 : 16, and rod-shaped nucleoli may

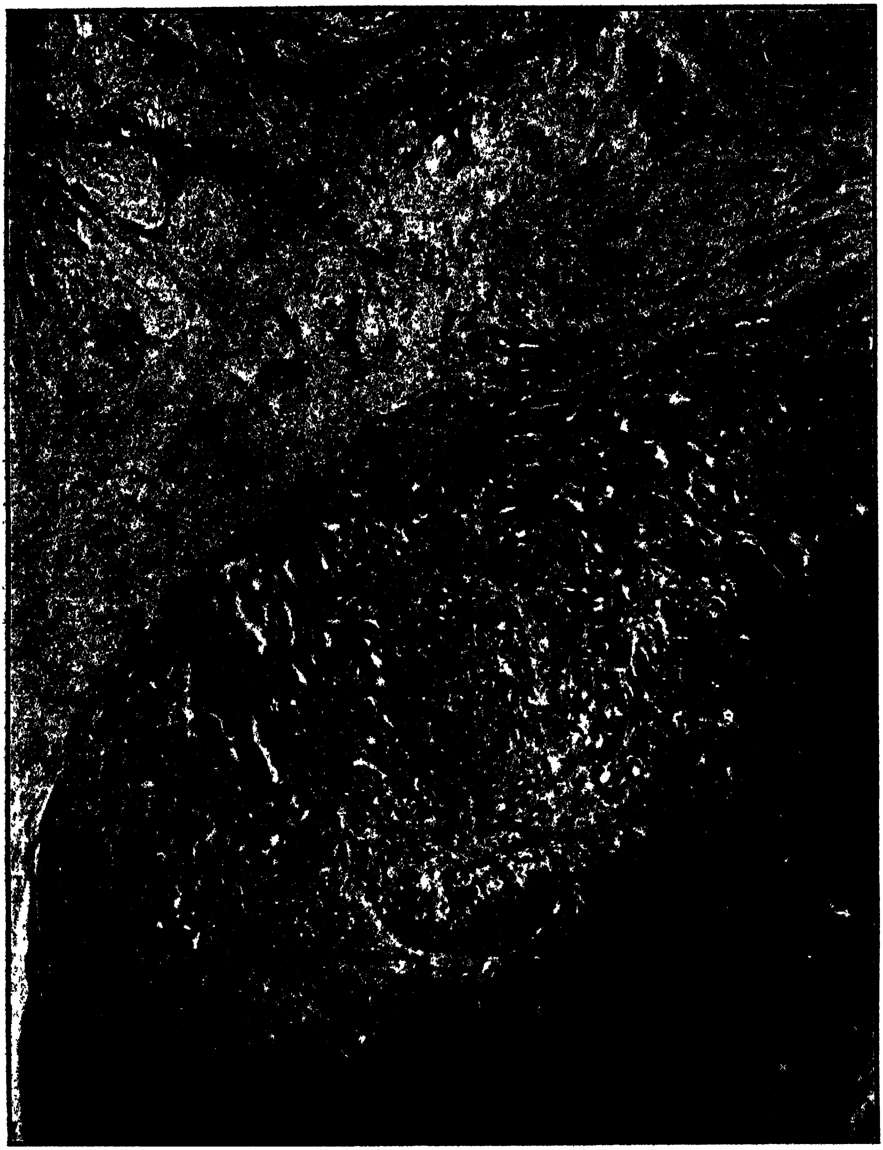

FIG. 42.—Transcoelomic implantation of the carcinoma shown in fig. 41: Above is seen the growth in the mesoduodenum as carcinoma leiomyomatosum; in the centre, the neoplastic tissue is seen to invade the pancreas as pure carcinoma. (15018; 60 ×.)

be seen. Some of the columnar cells are exceedingly tall and their nuclei centrally situated. Mitoses are in general more frequent than in the oviducal tumour.

Sections of the intestine, transecting the duodenal loop and pancreas, disclose extensive thickening of the walls of the bowel by more diffuse or more nodular subserous growths which do not

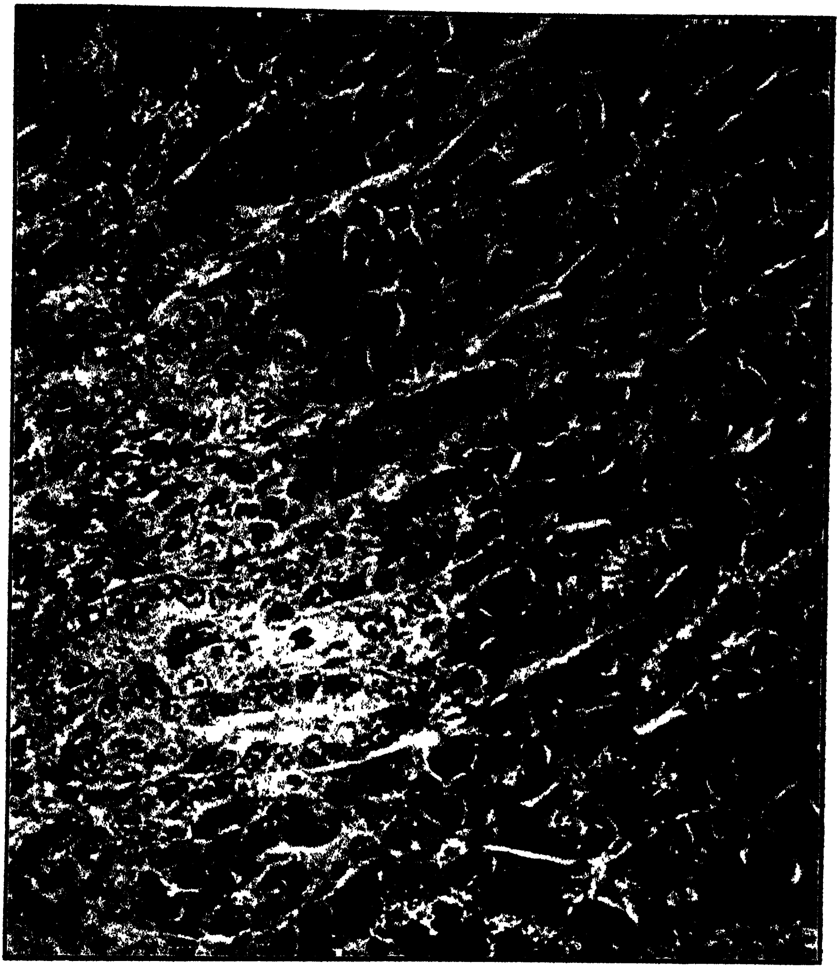

FIG. 43.—Detail of the pancreatic invasion shown in fig. 42: Establishment of intimate continuity between the neoplastic and the pancreatic acini, with appearances of transitions between the two tissues. (15018; 500 ×.)

invade the muscularis. Most of these nodular growths are to some extent encapsulated in the fibrotic subserosa, which is thickened to many times its normal dimensions. Within these connective-tissue capsules is a stroma predominantly or entirely of smooth muscle, enclosing aggregations of neoplastic epithelial tubules, whose columnar cells are similar to those of the oviduct tumour except that the zymogenic granulations are not seen (although a similar secretion may be present in the lumina) and that there is greater anaplasia, as shown here again by a less complete preservation of polarity, irregularity in nuclear size, and increased n : N ratio. In larger collections of neoplastic tubules, the individual tubules are separated by their connective-tissue stroma, but tubules lying singly are directly bordered by the muscular stroma. This isolation of elongated, ramifying strands of epithelium, often with no trace of lumina, in a large mass of muscular tissue is indeed a prominent feature. The picture may be aptly compared with that of a scirrhous cancer, except that here the stroma is not of connective tissue; as in a scirrhous, the epithelium is in many parts degenerate and atypical, having the appearance of being "squeezed out of existence" by the vigorous stromal reaction (cf. Fig. 44—from another case).

This neoplastic tissue of the bowel serosa continues into the mesoduodenum as a prominent muscular thickening across which the neoplastic epithelium straggles (Fig. 42, above) until, meeting the margin of the pancreas, it suddenly assumes a most vigorous growth (Fig. 42, centre). The excessive muscular stroma gives place to a small amount of connective-tissue stroma which supports masses of tubules and solid sheets of epithelium growing inwards and replacing the subcapsular portion of the pancreatic parenchyma in the form of small tongues which encroach into the organ to a depth of *ca.* 1 mm. at several points and from all sides. Here a peculiar phenomenon is observable which was considered of such importance that much care and time was expended in a study of the sections.—In many places the invading neoplastic tubules become continuous with the pancreatic alveoli: proceeding outwards from the pancreas, in one and the same alveolus the cells grade over from the normal (pancreatic) to the neoplastic type; or they may change suddenly, the neighbour of a normal pancreatic cell being a cell whose nucleus is twice the size and which has no deeply staining basal portion and no prominent peripheral area of acidophilic zymogen granules. Where the change is gradual, the appearance seen is as if the pancreatic cells themselves gradually acquire more hyperchromatic and larger nuclei, at first still retaining their characteristic cytoplasmic differentiation. This intimate continuity of the neoplastic with the pancreatic acini is shown in Fig. 42 and (especially) Fig. 43.

Sectons from other parts of the bowel show smaller nodular masses of tumour tissue in the subserosa. The liver, microscopically, shows pronounced diffuse fatty changes throughout the substance and, in addition, circumscribed foci of intense fatty changes. There are also the larger foci observed macroscopically and which are confined to the surface: these are neoplastic in nature and consist of the epithelial elements supported only by a fine connective-tissue stroma. There is no encapsulation, but invasion is limited and the nodules are fairly well circumscribed. The epithelial strands usually possess lumina which are often distended by retained secretion to form small cysts; the lining may be several cells in thickness; in other parts the epithelial cells grow in diffuse masses without lumen-formation or apparent polarity.

Discussion.—The following evidence favours the conclusion that in this case the largest of the oviducal tumours is the primary: it is the largest in size; the epithelial moiety of this musculo-epithelial neoplasm is closely similar in cytology and (tubular) arrangement (especially the zymogenic granulation and the staining reaction of its secretion) to the glands of the *propria mucosae* of the funnel; continuity of the neoplastic tubules with the normal glands is demonstrable; and in this tumour the anaplasia of the epithelium is more limited than in any of the others. (It must be remembered, however, that on account of the rapid growth of secondary implantations, it may be not at all easy to decide which of multiple tumours in the abdomen of a fowl is primary and which are secondary, and in reaching a decision in difficult cases a critical evaluation of the evidence obtained on microscopic examination, for example on the lines suggested above, is often essential).

From this oviducal tumour spread has occurred as follows: (*a*) to the intestinal and oviducal subserosa by transcoelomic implantation, (*b*) to the ovary by direct extension from implantations in the immediate neighbourhood of that organ (i.e. on the wall of the initial portion of the oviduct), (*c*) into the oviducal ligament in the vicinity of the primary tumour by direct extension, and (*d*) to the surface of the liver by transcoelomic implantation. In deciding the mechanism of spread to the liver the following had to be taken into account: haematogenous metastasis was a possibility because, although a penetration of veins had not been demonstrated in the tumours, the capacity for penetrative intravascular growth was proved by the invasion of ovarian lymphatics. Further, on macroscopic examination, multiple foci had been seen throughout the liver tissue in addition to the two (larger) ones confined to the surface and these had been presumed to be metastases of the neoplasm. Lastly, the liver surface is in our experience not very commonly the seat of transcoelomic implantation. However on microscopic examination it is seen that the hepatic secondaries are confined to the surface, the foci in the depths of the organ being all of the nature of circumscribed fatty infiltrations [cf. the "fatty infarcts" such as have been described by Cesaris Denil (1932) and Marras (1933) in the human liver. Such lesions were, however, not associated, as in this case, with diffuse fatty changes and are considered to arise as localised degenerative changes, following degeneration of a small branch of the hepatic artery. I find no previous record of their occurrence in domestic animals].

The neoplasm is to be termed a *carcinoma leiomyomatosum* ("leiomyoadenocarcinoma") and its dual histological nature is retained in all the secondary implantations except those in the liver and where the bowel implantations grow out to a distance from the intestinal wall in the mesoduodenum and invade the pancreas. It is considered that the moiety which undergoes implantation is the epithelial one: wherever such neoplastic epithelium is seeded it calls forth locally a proliferation of the pre-existing plain muscular tissue to provide a stroma: where no such pre-existing muscle is available, as in the liver, a connective-tissue stroma is substituted. Until this case was studied it did not appear beyond doubt that the retention of a mixed character in the secondaries of avian myoepithelial neoplasms might not be due to a simultaneous implantation of both epithelial and muscular elements, although, having regard to the "benign" character (not "leiomyo*sarcomatous*") of the muscle proliferation, this theory was *a priori* unlikely.

This case is further of importance in showing that ovarian tumours may be secondary to tumours of the oviduct. It has already been indicated that it is not always easy to decide on the primary or secondary nature of a given tumour nodule in the abdomen of the fowl, and only too many erroneous assessments in this regard are to be found in the literature. Now that it is becoming more widely realised how frequently peritoneal carcinosis is secondary to ovarian tumours, one observes a tendency to an overconfident assumption of the primary nature of any neoplastic lesion of the ovary that may be discovered in such cases. The lesson to be learned is that ovarian and bowel-serosal lesions may both be secondary to a primary in the oviduct. Such a primary is only too likely to be overlooked, (*a*) because the finding of an ovarian lesion (hastily considered the primary) satisfies the investigator and the rest of the organs may therefore be not subjected to such a close scrutiny at autopsy as would be the case if the primary was still to be demonstrated; (*b*) on account of the intramural type of growth, the tumour in the oviduct may produce an inconspicuous external enlargement of the organ, although its actual bulk may be large; and (*c*) because the oviduct, being a long and much convoluted organ is often not subjected to so thorough and close a scrutiny as it deserves. I find no mention in the literature that ovarian tumours may be secondary and have therefore thought fit to draw especial attention to this question. Further, all who are familiar with routine avian autopsy work know how often it occurs that a primary is actually not found (in the time available to the busy worker) to account for a secondary peritoneal carcinosis in the fowl. It appears most likely that in these cases, if a really competent examination of the ovary shows this organ to be negative, failure to demonstrate a primary depends on insufficiently close scrutiny of the (eighteen inch long!) oviduct.

The last observation regarding the pathology of this instructive case concerns the invasion of the pancreas from the mesoduodenal neoplastic tissue. In this connection we venture to point out the probability that many pathologists, confronted with the microscopic appearance of a limited field of this pancreatic invasion and not having fully studied the whole topographical distribution of the lesions, would (most excusably) diagnose a primary neoplasm arising from the pancreas. It is widely accepted as axiomatic that continuity is reliable evidence of histogenesis and in this case one could not wish for a clearer picture of what is usually regarded as histological continuity. Few pathologists appear to have ventured to criticise the truth of the axiom. Haythorn (1931), however, has in his study of the histogenesis of the basal-cell epitheliomas questioned the validity of the assumption that, because these growths may make contact with the epithelium of the overlying rete pegs, they have an origin from the latter; but even he is at some pains to contend that in this case not true continuity but a false continuity or mere contiguity (approximation) is what is seen; and he, like others, appears to accept as final the histogenetic implications of a demonstration of a " real " continuity. But long before this, Rous (1911a), in studying the fate of mixed grafts of adenocarcinoma and embryonic tissue into mice, had observed in some cases an " intimate relationship . . . in the direct union of tumour epithelium with the stratified squamous epithelium of the embryo . . . The cells were not merely juxtaposed, but were joined to one another and somewhat intermingled at the meeting point . . . Such a result is not always obtained; the normal and the neoplastic cells may be side by side, yet remain quite discrete . . . But when union does occur, the cells are sometimes intermingled to such an extent that *the one tissue may be said to pass into the other* (6), so far as this is possible of tissues quite unlike ". Further, Rous, on the basis of this observation, anticipated the very type of difficulty which has been described (and which has been also discussed by Haythorn in connection with the skin-tumours) saying " . . . if such a union can occur between normal and cancerous tissues of different type (i.e. squamous embryonic epithelium and glandular neoplastic epithelium) it would seem much more likely to take place between such as are similar, for example, between an epithelioma and the skin about it ". Yet, as he indicates, " the prevailing opinion among pathologists is still that continuity between normal and cancerous epithelium denotes, as a rule, and origin of the latter from the former, a histological gradation between them rendering this in individual instances quite certain ". Now this trend of pathological opinion is just as much in vogue to-day as when Rous uttered this warning. In recent times Welsh (1935) has gone to the other extreme in reviving the theory of spread of cancer by conversion of neighbouring cells, which is based largely on the observation of a continuity between cancerous and pre-existing epithelium (recognised of course as a continuity which does not denote origin), and which is bound up with the phenomenon of collateral hyperplasia. It is apparent, then, that the phenomenon of secondarily-established continuity is of the first importance in the study of the pathology of cancer, involving as it does the questions of both the histogenesis and the growth of tumours.

We have concluded from a study of this and other cases that as complete a continuity as could be desired to be seen may be a mere secondary one; not denoting histogenesis from, but merely the invasion of a pre-existing tissue: If such appearances are to be observed in the gradation between two tissues of different type, how much more confusing may they not be, as Rous anticipated, between normal and neoplastic columnar (glandular) epithelia of much the same type?

As we interpret the histological appearances of this pancreatic invasion, the following occurs:—The neoplastic tissue, penetrating through the capsule of the pancreas from the mesoduodenum, finds a pre-formed stroma, which (since that has always been its function) is highly suited to the support of glandular epithelial cells. The tumour cells, therefore, replace the pre-existing pancreatic cells in their own acini in such a progressive way that, for a time, one and the same acinus may be lined partly by neoplastic and partly by

(6) Italics mine.

normal cells. The presence of the neoplastic cells in immediate contiguity with the normal ones induces, as is commonly the case, the phenomenon of "collateral hyperplasia" in the latter. The result of this is that actual morphological gradations between the normal and the neoplastic cells come to exist and the appearance is one of "true" continuity. One should be cautious in assuming from this appearance that neoplastic cells are capable of influencing their normal neighbours in such a way that the latter actually become cancerized: although hyperplastic and atypical, their fate may yet well be that of ultimate replacement by and not of conversion to the neoplastic tissue. At the same time, one can see from a study of such cases that those who postulate a conversion of the cells are basing their theory on an acute observation which is by no means lightly to be dismissed.

The teaching of such observations is that continuity is not in all cases a trustworthy criterion of histogenesis, because *the continuity which denotes histogenesis may be completely imitated by the contiguity of invasion* plus collateral hyperplastic changes in the non-cancerous cells. In these cases, invasion by is to be distinguished from origin of cancerous tissue not on cytological grounds but on topographical evidence.

I have here contented myself with a discussion of the implications of this false continuity in general. But it should be pointed out that there are several special problems to which the principles enunciated should be applied. I refer to the vexed question of the histogenesis of the basal-cell carcinomas, based on their continuity with the overlying epithelium. This has been discussed by Haythorn, who was however inclined to consider that an admission of the existence of continuity would be fatal to his case. One would have preferred that he had admitted fully the appearance of continuity but denied its implication. And secondly I must refer to the obvious danger of diagnosing primary carcinoma of the pancreas in birds, in the absence of the fullest autopsy examination and consideration of the macroscopic and histological topography of the lesions: what appearances might result in a more advanced stage of pancreatic invasion by contiguous secondary neoplasms are easy to visualise on the basis of this study. The still wider implications of the principle of the continuity of invading tissues with normal tissues fall without the scope of this work.

Diagnosis.—Carcinoma (*adenomatosum et*) *leiomyomatosum* of the oviduct, with transcoelomic implantations on the oviducal wall, the ovarian bursa (whence direct extension to the ovary), intestinal wall, liver, and mesentery, including mesoduodenum (whence there is direct invasion of the pancreas with establishment of a continuity with the acini of that gland which must not be confused for evidence of histogenesis).

A further case of *carcinoma leiomymatosum* of the fowl is less satisfactory in that a complete autopsy protocol cannot be given, but it illustrates (better than does the preceding case) our introductory discussion of the nature and nomenclature of these tumours:—

(*Fowl*, 9313.)

The specimen consists of certain of the abdominal viscera of a hen. Macroscopically, the oviduct externally shows a dilatation of the isthmus, 4·5 cm. in length and irregularly oval in shape, apparently caused by a mass of firm consistence, lying within the oviduct. When the duct is opened, this enlargement is found to be caused, not (as was expected) by an egg concrement or retained ovum, but by a neoplasm, of the size mentioned, which is broadly attached to about half of the circumference of the mucosa and on section is seen to extend from beneath the serosa into the lumen, being altogether some 2 cm. in thickness, ulcerating, and leaving only a narrow slit-like space between its free surface and the opposed wall of the duct. In places also it extends completely through the subserosa, appearing on the exterior as flattened, inconspicuous, and but slightly elevated plaques. For a narrow area surrounding its broad base (which gradually thins into the wall of the oviduct) there is a covering of the mucosa (ridges); the greater part however presents a roughened, ulcerating surface protruding as described into the oviducal lumen. The consistence is firm, resembling smooth muscular tissue. Faint whitish centres in this tissue can be detected. The coils of the intestine are closely matted together by a thickened mesentery and are almost impossible to unravel in the preserved specimen. They show in places, especially in the region of the caeca, great thickenings of their walls apparently composed of smooth muscular tissue and reaching a thickness of 1 cm. There are also multiple, numerous, often confluent, pin-point to pin-head-sized, subserous, whitish nodules. Similar nodules are found on the mesentery and oviducal ligaments, and all the serous membranes of the abdomen are diffusely thickened. From the thickened ovarian bursa, there is a direct extension of the newly formed tissue into the ovary, in which it forms a central mass which branches peripherally among the normal and degenerated ova.

In sections of the oviduct and tumour, one sees that the free (inner) surface of the neoplasm has still a partial covering of the oviducal epithelium and actually only ulcerates at limited points: its greater part is covered by low villi of the mucosa, which are compressed against the opposite wall. In parts these villi have become atrophic and a non-villous covering of ciliated cells remains. Here and there this fades out completely and the underlying neoplastic tissue is exposed, having occasional ciliated cells still adhering to its surface. Occupying the *propria mucosae* in these parts is a neoplastic epithelium arranged for the most part as solid cell-masses with scanty connective-tissue stroma. In these masses lumina occur bordered by columnar to cuboidal cells with fairly distinct polarity. These lining cells are continuous (proximally) with the diffuse neoplastic epithelium, which shows loss of polarity, marked variation in nuclear size, and a distinct enlargement of nucleoli. Many of these diffusely arranged cells are spindle-shaped. Where the mucosa is not destroyed this neoplastic epithelium can be traced into continuity with the proprial glands, the nuclei of whose cells are much smaller (about half the size) and whose nucleoli are not prominent. As one traces the neoplastic tissue through the wall of the oviduct, i.e. from the mucosa region to the muscularis region, one sees that it becomes supported by a most excessive amount of stroma composed of branching and anastomosing bundles of smooth muscle cells. These bundles at first run rather obliquely with a tendency towards a circular arrangement (i.e. concentric with the oviduct lumen), while more externally they have a definite radial arrangement. This muscular tissue greatly predominates in the picture and between its thick strands the neoplastic epithelium occurs mostly as extremely elongated tubules with slit-like lumina or without visible lumina, although occasionally wider lumina occur. In many of the compressed tubules there is decreased cellular anaplasia and polarity is better preserved: the cell nuclei may be reduced in size as compared with those of the normal glands whence continuity was traced, and the nucleoli become less prominent. A small quantity of hyaline, acidophilic secretion may be found in the neoplastic tubules. The epithelial cells, where lining tubules, show a cuticular condensation of their distal borders. The newly-formed muscular tissue can be traced into continuity with the musculature of the duct wall, into which it passes without obvious demarcation: cytologically, the junction can however be recognised by the closer crowding and larger size of the nuclei of the newly-formed muscle cells, whose nucleoli are also slightly more distinct than in the case of the normal muscle.

The ovary is invaded by a diffuse growth of neoplastic epithelial tubules supported by smooth muscle stroma containing relatively small amounts of connective tissue. In places the tubules are closely aggregated, elsewhere dispersed in larger amounts of smooth muscle. There are also a leucocytic infiltration and cystic spaces containing degenerated yolk.

Sections from the greatly thickened bowel show a diffuse thickening semi-encircling the wall and composed of a large amount of smooth muscle tissue, at its edges continuous with both layers of the muscular coat, and containing relatively small amounts of the neoplastic epithelium. In the submucosa region, the muscular stroma can again be traced into continuity with the *muscularis mucosae*. There is also a limited invasion of the propria, in which however the neoplastic epithelium is supported by connective-tissue stroma, and in which the neoplastic parenchyma now dominates the picture. The overlying epithelium is atrophic and the lumen greatly reduced, but there is no ulceration. Other sections of the bowel show more circumscribed nodular lesions of the same general type, but where these are confined to the subserosa their stroma is formed by collagenous tissue. Sections through the vaginal portion of the oviduct show intramural nodules, rounded and well circumscribed, but not encapsulated, lying at the level of the circular muscularis. They consist of irregularly arranged bundles of plain muscle cells, at the edges continuous with the normal muscular coat, which stains more deeply with haematoxylin. Two of these nodules are *ca.* 1 mm. in diameter and do not completely occupy the thickness of the muscular wall, being covered inwardly by the normal circular muscle. A larger one (3 mm.) occupies the whole of the thickness of the muscular wall, being covered externally by serosa and internally by submucosa (see Fig. 45). Here also the structure is purely muscular, no epithelium being demonstrable. A section (previously cut at routine examination and whose exact point of origin could not be determined from the macroscopic examination) shows a stenosing lesion of the oviduct: centrally there is a small compressed slit-like lumen lined by pseudostratified ciliated epithelium resting on a propria containing a layer of glands and thrown into a few folds. Beneath the glandular layer is a muscularis which on all sides becomes confused with a neoplastic mass whose greater bulk is situated in the ligament of the oviduct. This neoplasm has a very imperfect and cellular capsule and surrounds the duct on all sides, although the duct lies eccentrically to it. It consists of a well-developed connective-tissue stroma enclosing many large bundles of irregularly-arranged smooth muscle cells and itself permeated throughout by neoplastic cuboidal to columnar epithelium. At one point the tubules formed by the latter reach to near the proprial glands but there is no invasion of the mucosa. Large parts of this neoplasm show necrobiotic changes; in large areas the epithelial moiety is minimal in amount (Fig. 44), forming a transition to the stage of complete regression shown in Fig. 45.

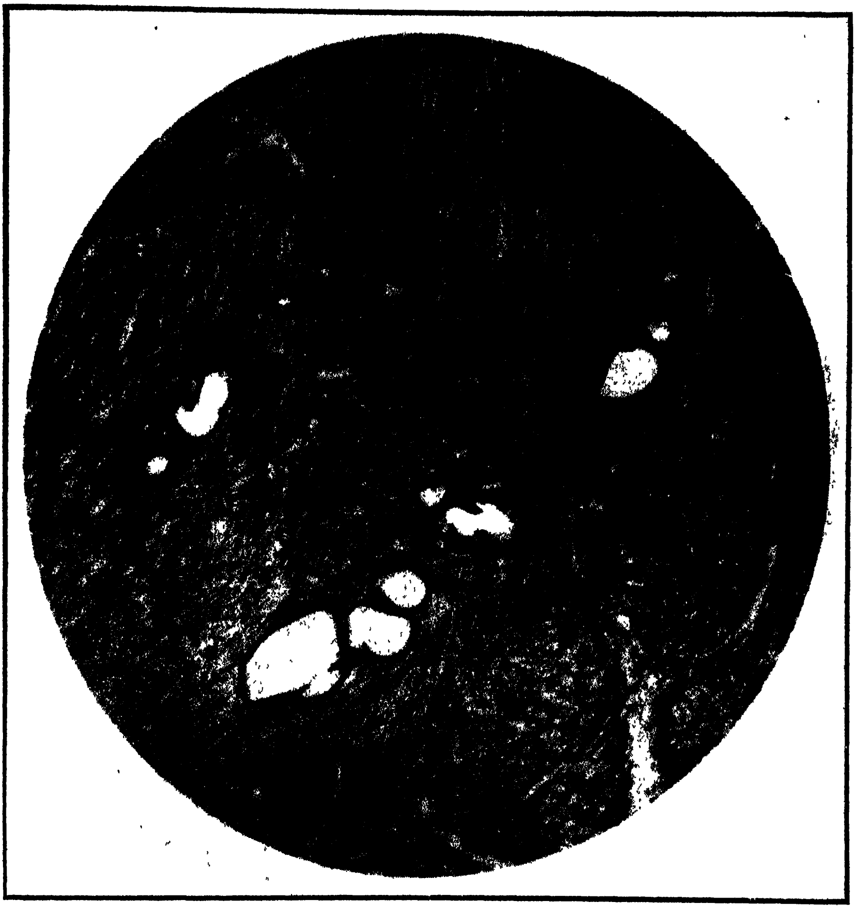

FIG. 44.—Structure of an implantation of carcinoma leiomyomatosum on the oviduct of a hen: Great preponderance of the muscular moiety with (incomplete) regression of the epithelial moiety. (9313; 75 ×).

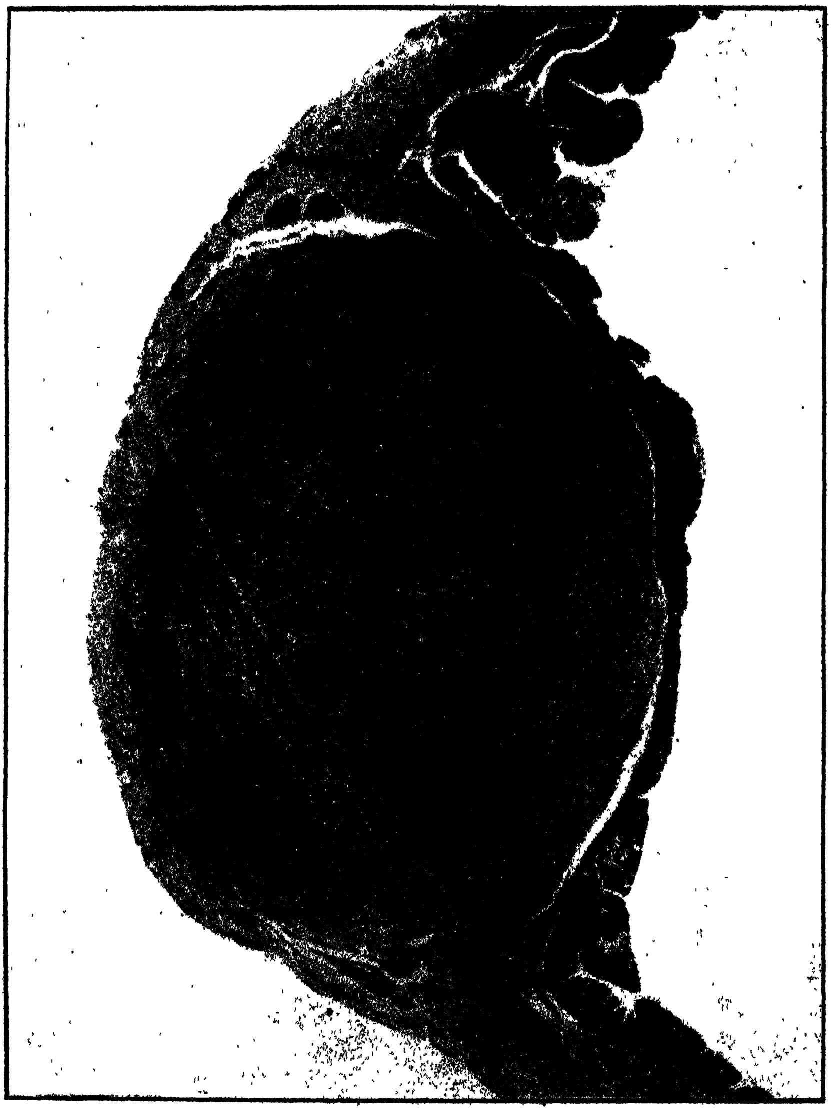

FIG. 45.—Another oviducal implantation in the same subject as fig. 44: Complete regression of the epithelial moiety of carcinoma leiomyomatosum resulting in a purely leiomyomatous structure. (9313; 30 ×).

Discussion.—The above described appearances are interpreted as follows:—The epithelial moiety of this tumour arises from the glands of the oviducal propria and grows as a pure *carcinoma adenomatosum* in the propria, through which it ulcerates and causes a severe stenosis. Growing also outwards, it meets the muscular wall of the duct, which, as it becomes invaded, proliferates to provide a stroma for the epithelial elements. This phenomenon was illustrated by Fig. 41, in the previous case. The serosa is pentrated and the epithelial elements become implanted on other organs and on other parts of the oviduct, where they again stimulate a growth of pre-existing muscle as soon as they have penetrated further than the serosa of the organs concerned. The purely muscular nodules (Fig. 45) to be found in parts of the oviduct are to be interpreted as originally cancerous implantations in which the excessive muscular proliferation has been successful in causing regression of the epithelial moiety. Indeed this process can be seen in progress in a study of other of the nodules (Fig. 44) and it appears that, prior to its regression, the neoplastic epithelium loses its morphological anaplastic qualities. The fact that the development of the muscular element may, judged by its results, be actually a purposeful or at least a useful reaction of the organism influences one in deciding (as previously discussed) not to regard this proliferation as of a truly neoplastic nature and the tumours as mixed tumours; for as is well known, the essence of the neoplastic process is its lack of contribution to the bodily economy (⁷). At the same time, the newly-formed muscle has histologically and cytologically a quite neoplastic appearance, and it differs, as has been said from the normal; it is thus not certain whether it is equivalent to ordinary hypertrophic muscular tissue.

This case is important in allowing the following generalisations to be stated: (*a*) that in a "mixed" tumour (the term is used subject to the reservations aforestated) the one element may, preceding the other in time of formation, become secondarily associated with the later-formed moiety, whose proliferation is directly referable to a stimulation exerted by the growth of the first-formed moiety; (*b*) that in such a tumour the one element may, by over-growth, cause regression of the other (malignant) element and in this respect have the features of a protective and not a "purposeless" reaction, such as is usually associated with neoplasia.

In conclusion, it may be remarked that failure to observe mitotic figures in the large numbers of sections examined shows the unreliability of the mitotic index as a criterion of the malignancy of these avian neoplasms.

Diagnosis.—*Carcinoma leiomyomatosum* of the oviduct, with multiple implantations on the abdominal viscera and mesentery and with invasion of the ovary. Some of the secondaries have a purely leiomyomatous structure, owing to regression of the carcinomatous cells.

(⁷) This classical conception, however, obviously needs revision in view of observations on the function of neoplastic thyroid tissue in man.

(3) *Carcinoma of the Pharynx.*

Apart from Feldman's (1932) statistical mention of a single case of pharyngeal carcinoma in the fowl (which he does not describe) no reference to this disease was found in the literature, although acanthoma of the oesophagus has been reported by Joest and Ernesti (1916). In South Africa a single case of pharyngeal carcinoma has been encountered:—

(*Fowl*, 14035.)

The specimen consists of the pharynx of a White Leghorn hen. There is a large flattened-oval mass occupying the pharyngeal wall and ulcerating into the lumen. It measures 5 by 4 cm. and occupies the whole lumen of the organ, being 2 cm. in thickness. It has the dense elastic consistence of smooth muscle and contains (to the naked-eye) elongated strands of a softer and lighter-coloured tissue.

Microscopically, the neoplastic tissue is seen to replace all the layers of the wall of the pharynx, being at the edges covered by the pharyngeal epithelium and elsewhere ulcerating through the mucosa. It consists (Fig. 46) of an epithelial moiety which, as it is traced outwards from the submucosa, becomes associated with a progressive increase of a leiomyomatoid stromal moiety apparently derived from the pre-existing musculature. This, in the greater part of the tumour, preponderates over the epithelial entity, as has been described previously in the leiomyomatous carcinomas of the bird. The neoplastic epithelium is of an ambiguous nature: for the most part it is little differentiated and resembles glandular more than squamous epithelium, although there is no distinct lumen-formation. These cells bear some considerable resemblance to the normal elements of the deeper (basal) layers of the mucosa. But in many places distinct differentiation to squamous elements occurs and limited keratinisation is seen. The neoplastic epithelium shows an average n : N ratio of 1 : 9 (cf. maximal ratios of *ca.* 1 : 14 in the pharyngeal mucosa). Mitoses are fairly frequent. There are further to be seen accumulations of lymphocytes closely associated with the neoplastic tissue.

Remarks.—This tumour, like those which have been described in the reproductive organs of fowls, is associated with a pronounced smooth muscular stroma whose development approaches a neoplastic grade. Regarding the essential (epithelial) moiety of the tumour, the type of growth offers a close parallel to those tumours of mammals which are known as transitional-celled carcinomas; a further resemblance is seen to the latter in the presence of groups of lymphocytes in the neoplastic tissue. Such tumours of mammals will be dealt within the following section.

Diagnosis.—(Transitional-cell) *carcinoma leiomyomatosum* of the pharynx.

CARCINOMA OF THE DOMESTIC MAMMALS.

The 28 cases of mammalian carcinoma in which primary lesions were submitted (excluding those arising from squamous epithelium and its derivatives) have the following organ distribution: liver—16 cases, lung—3 cases, testicle—2 cases, mammary gland—1 case

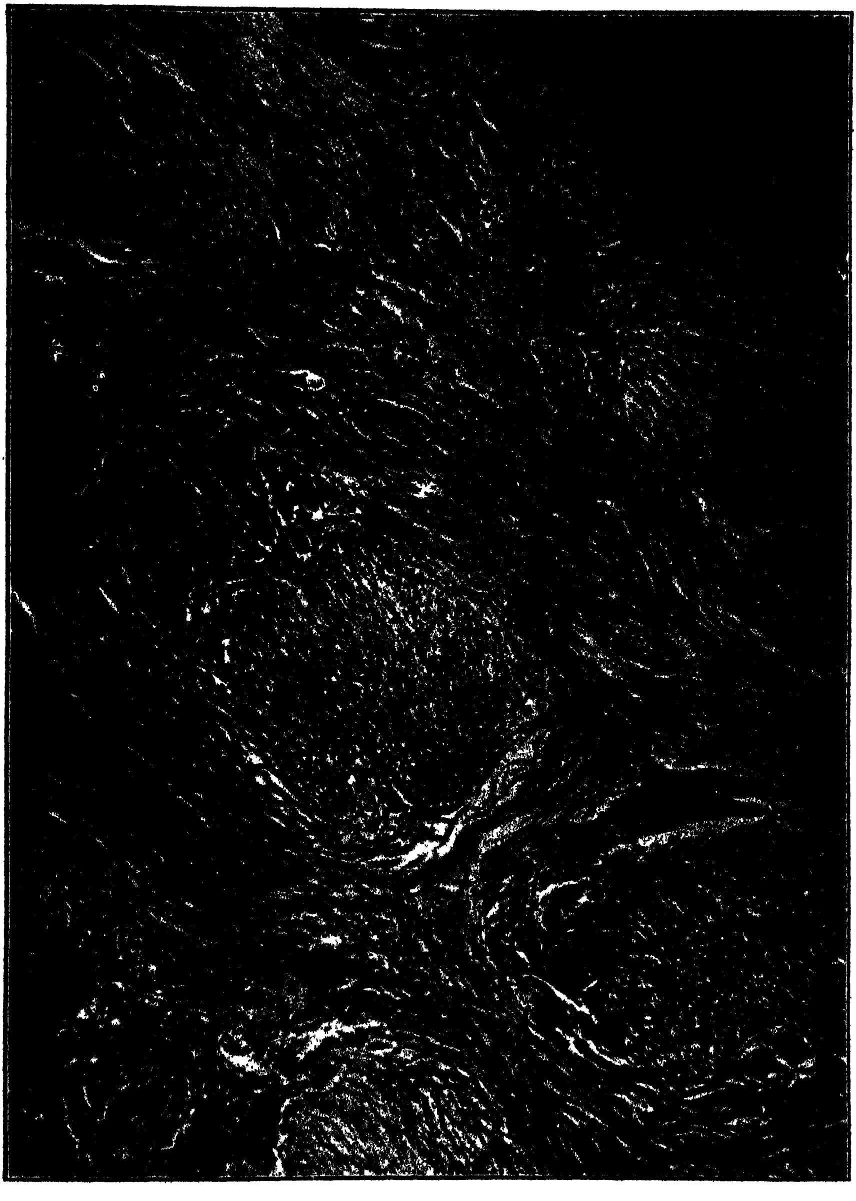

FIG. 46.—Carcinoma leiomyomatosum of the pharnyx of a fowl. (14035; 100 ×).

(excluding one case in the rabbit). stomach, pancreas, small intestine, parotid salivary gland, kidney, and anus (anal glands)—one case of each. There are also 4 cases of transitional cell carcinoma of bovines which are discussed later. Examples of liver carcinomas are confined to the ruminants and the dog and are to be discussed in another chapter (IV). The mammary tumour was found in a mule. I have debated considerably as to the advisability of including here several further tumours of the dog's breast; these contain, in addition to an epithelial moiety, an element (osteomatous, chrondromatous, sarcomatous, etc.) of mesenchymal derivation. On consideration, these have all been classed with the mixed tumours, although we have found that in some of the cases regarded for practical purposes as pure carcinoma, it is not always easy to decide whether all the neoplastic elements are to be regarded as of epithelial derivation. In other words there appear to exist gradations between pure carcinoma and mixed tumours with an epithelial element. The same difficulty exists in human pathology, in which spindle-shaped cells may occur in mammary tumours, usually referred to (e.g. Ewing) as " embryonal carcinomas ". It would appear that most of our cases of canine breast carcinoma fall into a similar category, although to what extent the term " embryonal " is literally justified it is difficult to say.

From the cases of carcinoma in the collection the following less well known or hitherto undescribed tumours have been selected for discussion :—

Carcinoma of the Stomach of the Horse.

The only cases of (glandular) carcinoma of the stomach of the horse which have up till now been reported are those ot Roloff (1868) and Sturm (1889); the latter author, according to Joest, erroneously diagnosed his tumour as adenoma. Acanthoma arising from the oesophageal portion of the gastric mucosa and therefore comparable not with gastric carcinoma but with epithelioma ot the oesophagus of man and with acanthoma of the fore-stomachs of ruminants is of more frequent occurrence [cf. Sticker's (1902) 8 cases among 311 equine carcinomas]; they have not ,however, been encountered among equines in this country. In view of the great rarity of true gastric carcinoma, the following case is of interest :—

(*Equine*, 15193.)

The subject was an aged horse, destroyed in Johannesburg, and from which formalin-fixed specimens were kindly collected for me by Dr. G. Martinaglia. The specimen consists of the following :—Two pieces of the stomach wall, of which the first includes the *margo plicatus* with a portion of oesophageal and glandular mucosa on each side of it (Fig. 47). The wall is diffusely infiltrated by a soft, white growth, which for the most part occupies the submucosa, the muscularis, and the subserosa, but in one part ulcerates through the mucosa to form an irregular fungating mass about the size of a crown-piece. On the outer aspect (Fig. 48), the growth appears in the form of multiple nodular outgrowths some of which are covered by the serosa and which vary from ·5 to 5 mm. in diameter, sometimes much larger owing to confluence. The growth is essentially intramural, therefore, and the wall is thickened to as much as 3·5 cm. The second piece of stomach is from the oesophageal portion of the organ: here the wall is also infiltrated, but no ulceration occurs. As the two pieces do not fit together, it is not possible to give the exact size of this large, flattened, intramural tumour, but it must have affected an area at least the size of the hand. Further, there are fragments of the large intestine bearing multiple subserous nodules 1 to 5 mm. in diameter; of liver with multiple non-encapsulated white foci, 1 mm. to 1 cm. in diameter, which irregularly infiltrate the hepatic parenchyma; of lung with a single infiltrating nodule *ca.* 5 mm. in diameter; and of omentum or mesentery which is diffusely thickened by multiple, confluent nodules of small size.

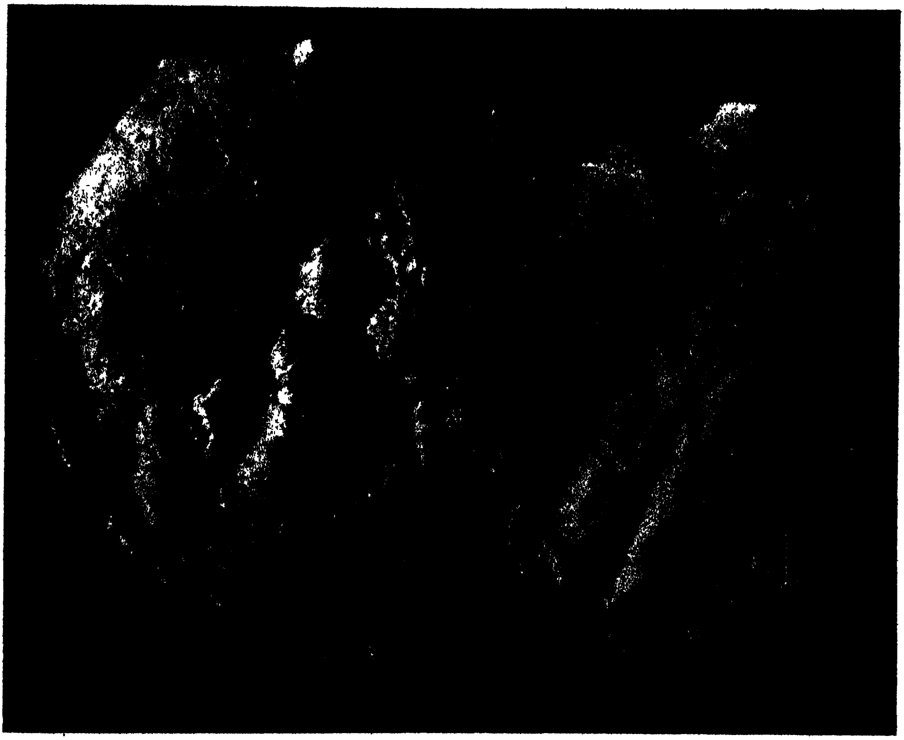

FIG. 47.—Carcinoma of the stomach of the horse: Right, the *margo plicatus* and the oesophageal portion of the mucosa; left, intramural and ulcerating growth of the tumour in the *pars glandularis.* (15193: nat. size.)

Sections of the stomach (Fig. 49-52) show the presence of a new-growth composed of an irregularly columnar type of epithelial cell arranged in elongated cords and strands and separated by a relatively small amount of cellular connective-tissue stroma. This neoplasm in one part occupies the mucosa and reaches the surface thereof in the fundus gland region. At its circumference it grows infiltratively in the mucosa (Fig. 49), without definite demarcation from the neighbouring glands; the latter show considerable irregularity (hypertrophy and multiplication of cells) and in many places an apparent continuity can be traced between these glands and the neoplastic elements. The gastric mucosa shows fibrosis and atrophy (chronic atrophic gastritis) except at the margin of the neoplastic tissue where there is (collateral) hypertrophy. From the mucosa the neoplastic tissue infiltrates outwards through the *muscularis mucosae* and the submucosa in the form of thin strands which are continuous with large nodules and strands occupying the muscularis (Fig. 50) and subserosa. At the base of the ulcerating portion, the submucosa is much thickened and indurated by collagenous connective tissue and here it is seen that the tumour cells are obviously extending in strands through the lymphatics, so that a ramifying plexus of neoplastic epithelium is formed. The tumour cells (Figs. 51 and 52) have almost completely lost their polarity, they show considerable irregularity of size and shape; many of the nuclei are hyperchromatic, and some show enlarged nucleoli. They tend to be larger than the normal gland cells of the fundus, and more especially their nuclei, which may be two or three times the normal size. There is some tendency for the outer cells of each nest to be arranged perpendicularly to the connective-tissue stroma, but almost as many lie irregularly, while the inner cells are in quite disorderly arrangement. There is scarcely a trace of lumen-formation. The scanty stroma forms a delicate but rich meshwork of considerable regularity, so that the strands of neoplastic cells are of the dimensions of the normal acini of the fundus region. In places the borders of the intramuscular nodules show an imperfect encapsulation, but more often there is no protective connective-tissue reaction. Here and there necrosis has overtaken individual alveoli. Mitoses are numerous (index = 3).

Fig. 48.—External aspect of the stomach wall shown in fig. 47: Penetration of the serosa and intramural growth of gastric carcinoma. (15193; nat. size.)

The mesentery and omentum, microscopically, are seen to be affected by confluent nodules, imperfectly demarcated by strands of connective tissue and which are of similar morphology to the gastric tumour. These nodules infiltrate and replace the subserous adipose tissue. Anaplasia is here somewhat more advanced, cell polarity being scarcely at all recognisable and a few multinucleate (tumour) giant cells occurring. The finer stroma separating the adjacent alveoli is less differentiated and smaller in amount than in the tumour of the stomach. The lung nodule consists of a number of rather distinctly separated and solid nests of anaplastic epithelium lying in preformed spaces which show traces of endothelial lining (lymphatics). Occasionally polarity is not completely lacking and

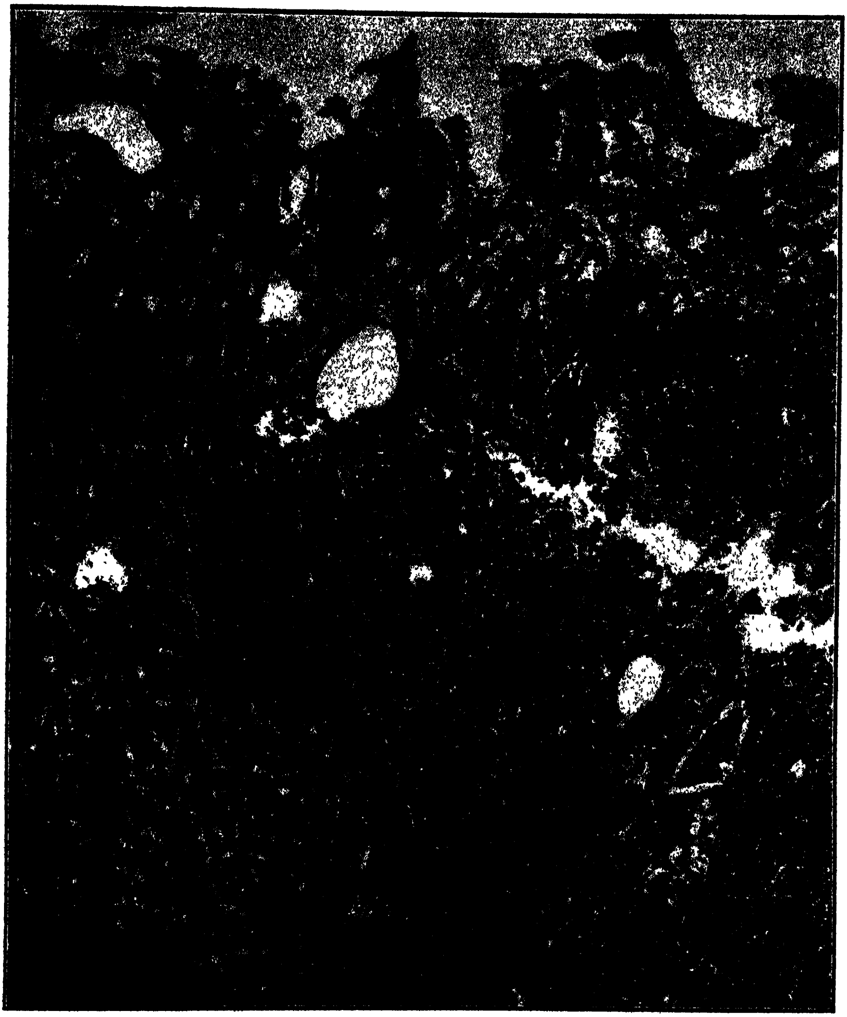

Fig. 49.—Gastric carcinoma of the horse : Invasion of the gastric mucosa. (15193 ; 60 ×).

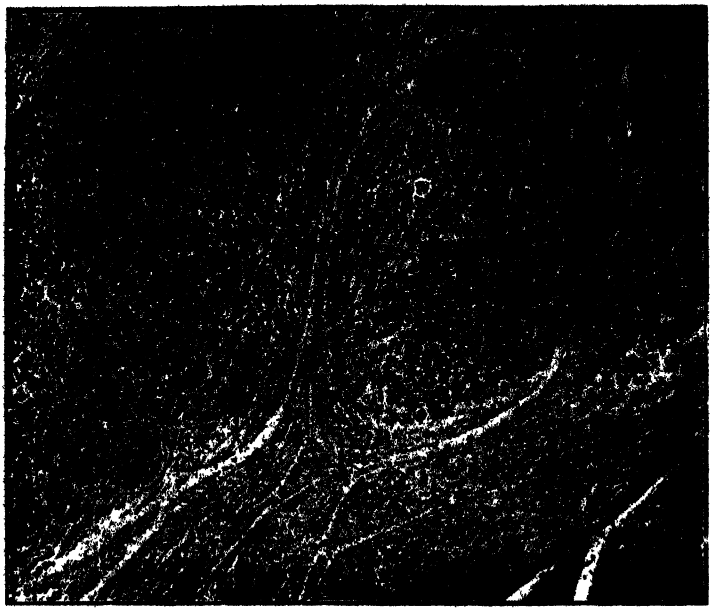

FIG. 50.—Gastric carcinoma of the horse: Intramural growth invading the muscularis. (15193; 60 ×).

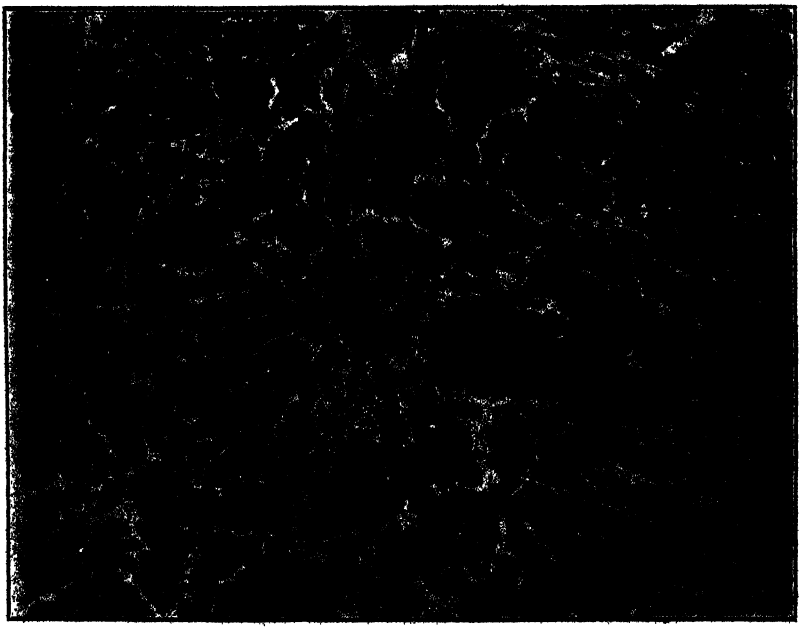

FIG. 51.—Gastric carcinoma of the horse: Anaplastic growth and little lumen-formation (15193; 250 ×).

there may be traces of lumen formation. Some of the cell-nests are necrotic. There is no circumscription, and many outlying islands of tumour cells occur. There is little stromal reaction. The liver nodules (Fig. 53) are composed of an infiltrative growth of solid strands of the tumour cells. The portal veins in Glisson's capsule are largely occluded by the neoplastic cells, and show a narrow peripheral space in which blood (rich in neutrophiles) still circulates. From here strands pass between the liver cell columns towards the centre of the lobule, obliterating the sinusoids and destroying the hepatic parenchyma, the surviving liver cells showing pronounced signs of degeneration (hyperchromatosis, chromatolysis, fatty changes). Here and there are large globules of acidophile hyaline material apparently formed by degeneration of the neoplastic cells. There is scarcely any connective tissue reaction. The Kupffer cells in these areas are richly pigmented.

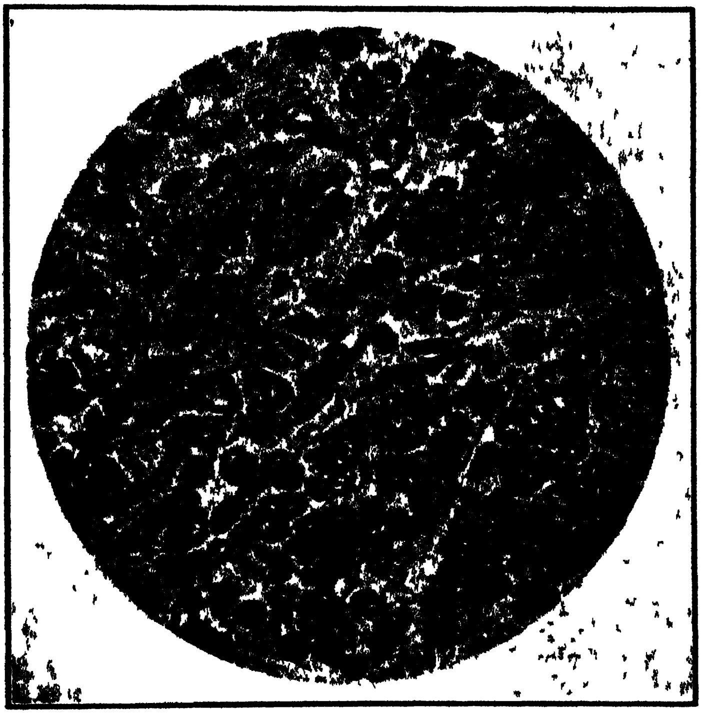

FIG. 52.—Gastric carcinoma of the horse: Detail of the structure of the more anaplastic portions. (15193; 500 ×).

Diagnosis.—Carcinoma medullare of the stomach with transcoelomic implantations to the serosae and with metastases to the liver and lungs.

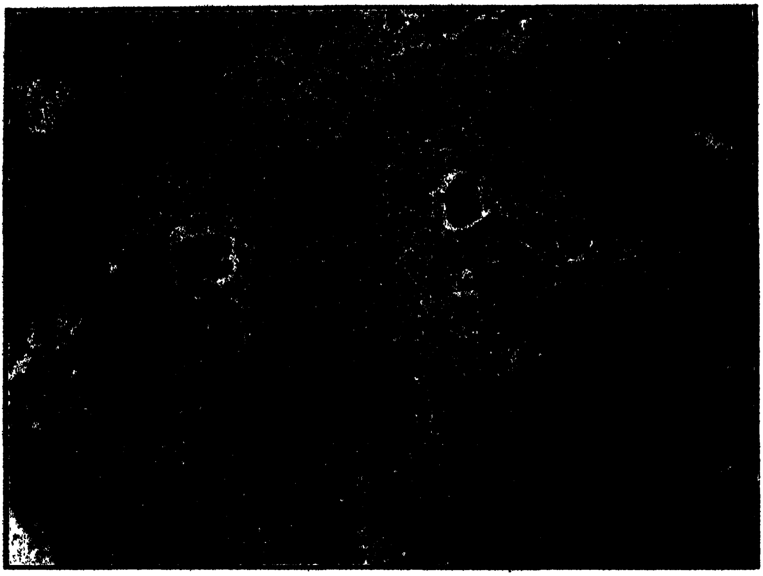

FIG. 53.—Hepatic metastases of carcinoma of the stomach of the horse: Tumour emboli commencing to invade liver parenchyma from the portal veins. (15193; 30 ×).

Carcinoma of the Small Intestine of the Sheep.

Known to occur, although rarely, in all domesticated species except the small ruminants and the pig, carcinoma of the intestine is a hitherto unrecorded tumour of the sheep, a species which is considered "to be relatively immune to carcinomatous proliferation" (Feldman, 1932). The Onderstepoort collection contains the first recorded case of this disease:—

(*Ovine*, 4144.)

The specimen consists of a portion of the small intestine of a sheep. This shows (Fig. 54) a sausage-shaped tumour protruding into the lumen and measuring 4 cm. in length and 1·3 cm. in diameter. It has a lobulated, ulcerating surface and is fairly firm in consistence. At its point of attachment to the bowel wall it causes a stenosis, infiltrating intramurally below the mucosa in the form of an annular band. Proximally to this point the bowel is much dilated (to about twice its normal diameter) and the muscularis is seen to be hypertrophied. In this region the serosal aspect of the intestine is irregular owing to the presence of multiple, ill-defined, confluent elevations of the size of a pin's head.

Microscopically, sections of the intramural part (Fig. 55) of the tumour show an invasion of the *propria mucosae* by the neoplastic tissue which is replacing the latter and which consists of acini of glandular epithelial cells whose cytoplasm is filled with droplets of mucus. These cells break through the *muscularis mucosae*, penetrate the circular muscularis in the form of radially directed strands, and to a lesser extent also the longitudinal muscularis, finally reaching the subserosa. The stroma is delicate. Sections through the intra-enteral portion of the growth show a richer connective-tissue stroma in which the neoplastic alveoli tend to be smaller and more widely dispersed. The neoplastic cells are often so distended with mucus that they assume the well-known "signet-ring" forms, having compressed, eccentric nuclei. The n : N ratio does not exceed *ca.* 1 : 16 and mitotic index is 2. Other sections show a diffuse infiltration of the subserosa of the bowel above the point of stenosis; the muscularis is greatly hypertrophied.

Diagnosis.—Colloid (mucoid) carcinoma of the small intestine.

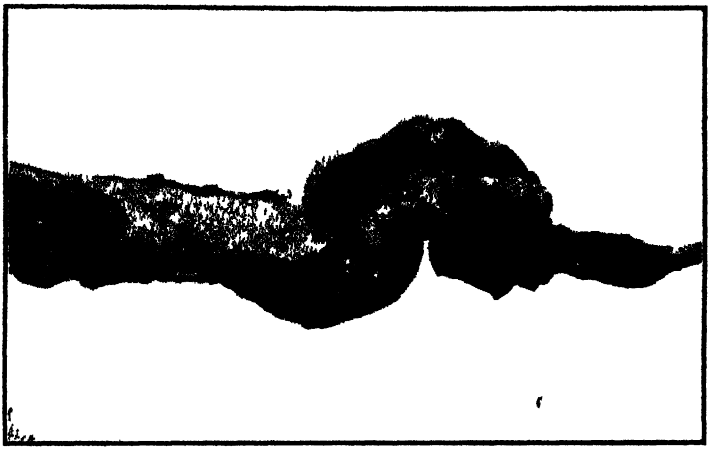

Fig. 54.—Carcinoma of the small intestine of the sheep: Right, the tumour protruding into the lumen and also growing intramurally in the bowel wall; left, the dilated bowel cranial to the point of stenosis. (4144; 1/2 ×).

Carcinoma of the Pancreas of the Sheep.

Carcinoma of the pancreas is a rare disease in domestic animals and has not been reported in the sheep. The following case was encountered:—

(*Ovine*, 6704.)

The subject of this tumour was a "full-mouth" Persian ewe. A complete description of the lesions encountered at autopsy cannot be given because the tumour foci were mistaken for abscesses and therefore not very closely described. The specimen consists of a slice of a walnut-sized "abscess" in the pancreas, a portion of the liver which was stated to have contained numerous foci "of muco-purulent nature" and a portion of lung stated to contain "foci of purulent material". The spleen was also affected and the peritoneal cavity contained 250 cc. of turbid, greyish fluid in which were suspended "yellowish, purulent floccules". Only the microscopic preparations were available to me for examination:—

The pancreas contains an encapsulated tumour (Fig. 56) within its substance and although intravascular invasion can be seen in the thick layer of connective tissue which surrounds the neoplastic tissue,

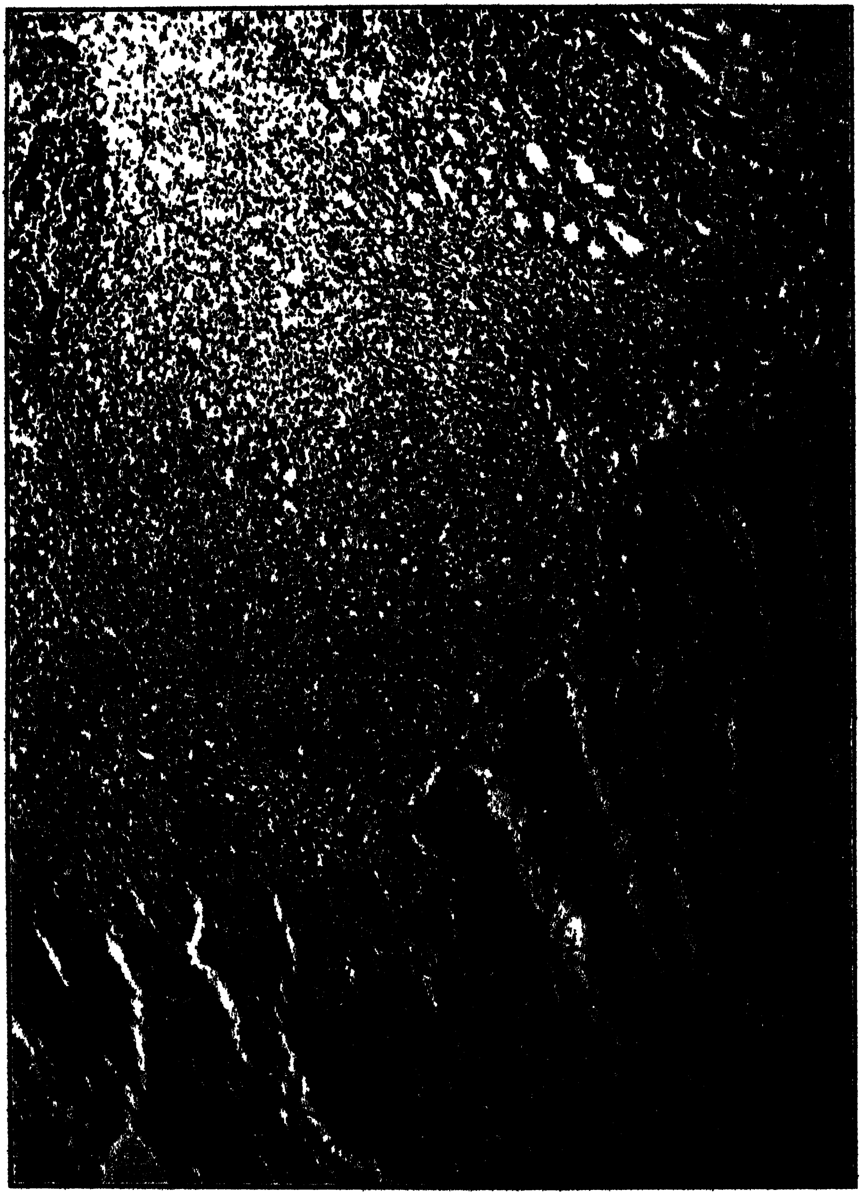

Fig. 55.—Intestinal carcinoma of the sheep: Above, invasion of the mucosa; below, strands of tumour tissue penetrating the circular muscularis. (4144; 60 ×).

the pancreatic parenchyma is not directly invaded. The neoplasm consists of a fairly well developed connective-tissue stroma rich in fibroblasts and in most parts heavily infiltrated by lymphocytes; this supports epithelial-lined acini of very variable size, most of which are distended into small cysts by their content of necrotic debris derived from the desquamated cells. More solid areas of similar neoplastic cells also occur. The neoplastic epithelium is usually of simple columnar to cuboidal type and where polarity is preserved the nuclei are located proximally (i.e. remote from the lumina), leaving a distal free area of cytoplasm which stains more acidophilic than the rest of the cell (cf. the normal pancreatic cell).

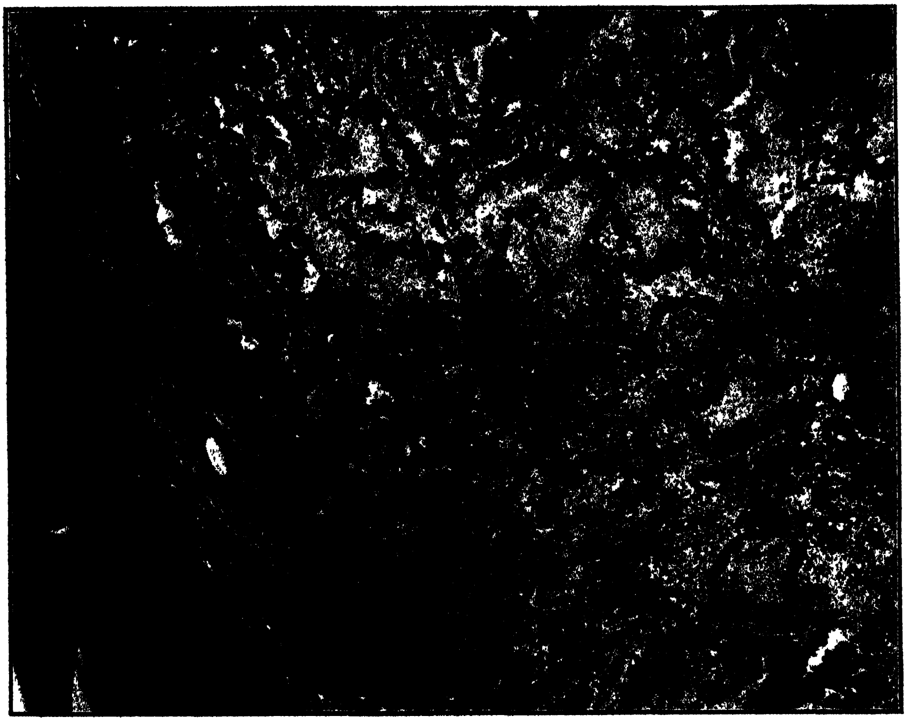

FIG. 56.—Carcinoma of the pancreas of the sheep: Left, encapsulation against the normal pancreatic tissue (extreme left) with invasion of the capsule. (6704; 32 ×).

The cells are variable in size but usually very much larger than the normal pancreatic elements. The nucleoli (often double) are clearly enlarged and the average n : N ratio is *ca.* 1 : 9 (cf. the pancreatic cells—1 : 25 or 1 : 30); it may reach 1 : 5. All signs of anaplasia are well marked: hyperchromasia of the nuclei, great variability of nuclear size, presence of multinucleate neoplastic giant cells, and many mitotic figures. Both the liver and lung contain foci of the same nature, except that they are unencapsulated.

Remarks.—Although one is cautious of diagnosing primary carcinoma of the pancreas in view of its rarity in animals, the absence in this case of any other lesion which might be primary to these tumours, the resemblance of the neoplastic cells to those of the pancreatic parenchyma, and the fact that the pancreatic tumour is encapsulated while those of the liver and lung, taken to be secondary, are not, appear to be adequate grounds for confidence regarding the nature of the lesions. The failure to recognise the neoplastic nature of the disease at post-mortem is of practical importance and is explained by the retention of necrotic contents by the neoplastic glands, thus simulating a suppurative process. A feature of the case is the extensive metastases from a relatively small primary, explicable on the grounds of the pronounced intravascular invasive tendency of the latter.

Diagnosis.—Carcinoma of the pancreas with pulmonary, hepatic, and (not confirmed microscopically) splenic metastases.

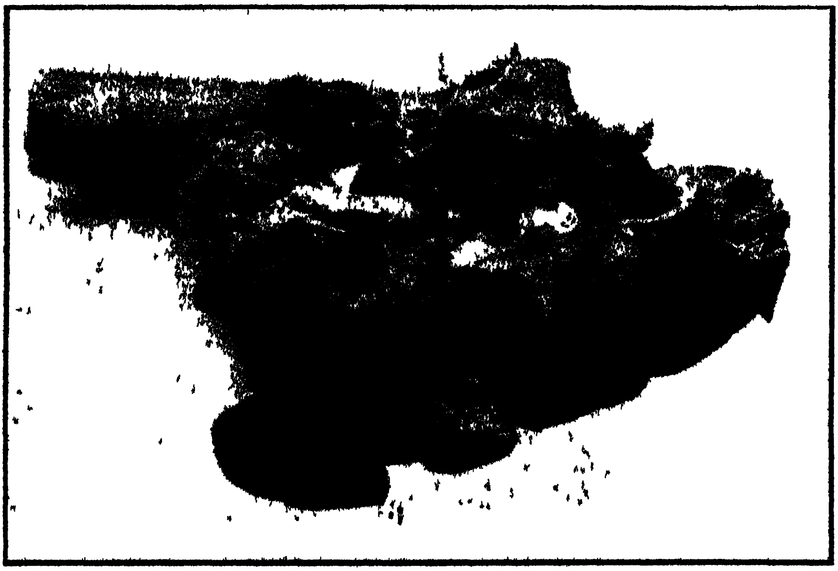

FIG. 57.—Primary carcinoma of the lung arising from the intrapulmonary bronchi in the dog: Primary growth surrounds the larger bronchi to right of centre of illustration; to the left, metastases in the bronchial lymph-nodes. (14574; 1/2 ×).

Carcinoma of the Lung.

Primary carcinoma of the lung has been reported in nearly all species of domesticated animals, but is considered a rare disease. The Onderstepoort collection contains three examples, which need not be described in detail. Two of the cases concerned the dog and the third a sheep. The canine cases illustrate well the differentiation which, in lung carcinoma of animals as well as of man, must be made between the two chief types, viz. those arising from the intrapulmonary bronchi and those considered to have their origin from the pulmonary parenchyma. The macroscopic appearance of the bronchial type is shown in Fig. 57, from a dog—(Canine, 14574)—which had to be

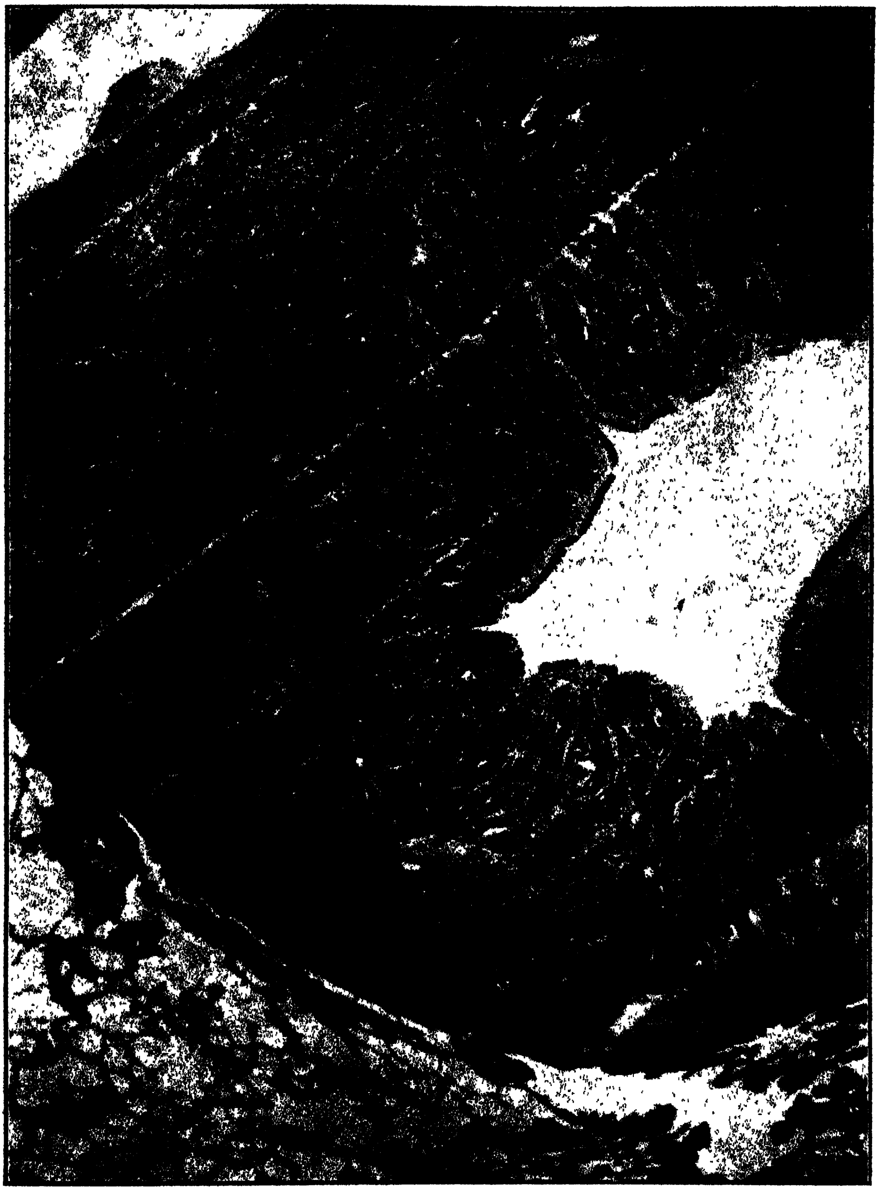

FIG. 58.—Microscopic characteristics of the bronchiogenous carcinoma of the dog (fig. 57): Growth in the wall of a bronchus, with intact lining. (14574; 32 ×).

destroyed on account of chronic dyspnoea: the right lung will be seen to be affected by a diffuse neoplastic mass surrounding the main bronchus of the diaphragmatic lobe and following its chief branches into the substance of the lung. It is a stenosing lesion, without ulceration. Metastases were recorded in the bronchial and inferior cervical lymph-nodes, and in the liver, periportal lymph-nodes, and spleen. Microscopically (Fig. 58) the structure of this type of tumour is briefly as follows:—The neoplastic tissue is mainly confined to the walls of the bronchi and invades the blood-vessels which accompany them; the bronchial epithelium remains intact. There is also invasion of the neighbouring pulmonary parenchyma, where the cells show extreme anaplasia. Here intranuclear "inclusions" occur similar to those considered to arise from the nucleoli and one of these was the largest encountered in any tumour, measuring 25μ in diameter; anaplastic cells may reach a diameter of as much as 120μ. In this case there were no definite features (mucus production by the cells) whereby one could conclude with certainty that the tumour arose from the bronchial mucous glands, but the cells are glandular in nature and one is probably justified in assuming that the growth corresponds with those of the human lung believed to have such origin and which are characterised by "limitation chiefly to the walls and especially to the submucosa of the bronchi; relatively intact condition of the bronchial lining; stenosis rather than dilatation of the bronchi; often considerable infiltration of the parenchyma . . ." (Ewing)—all of which are features of the case described.

The second type of pulmonary carcinoma is illustrated by Fig. 59, a lesion from the lung of a fox terrier (6631) which died with symptoms of severe dyspnoea a short time after the onset of clinical symptoms. Microscopically, there is peribronchial growth with ulceration into the lumina of smaller bronchi and perivascular growth (within the lymphatics of the adventitia of blood-vessels); but chiefly there is an extensive spread in the pulmonary parenchyma. The neoplastic tissue is of two types, with all grades of transition: (*a*) adenoid acini lined by tall cylindrical cells and more solid alveoli with loss of cell polarity; (*b*) squamous cells with intercellular bridges (prickle cells) which undergo individual keratinisation and also form occasional small pearls. The rest of the lung is affected by acute catarrhal pneumonia, doubtless the immediate cause of death. The diagnosis is adeno-acanthoma (carcinoma), a type of tumour usually considered to arise from the pulmonary alveoli.

It is not proposed to deal in detail with the solitary case of pulmonary carcinoma encountered in a sheep. The lesions consisted in multiple foci (varying from 1 cm. to 1 mm. in diameter) some of which were circumscribed and some not. There was also confluence to form areas measuring over 4 cm. in diameter. The structure was mainly that of papilliform adenoid carcinoma resembling the lesions of jagsiekte but able to be differentiated on account of areas with loss of lumen formation and complete loss of cell polarity; it is mainly on account of the importance of this differential diagnosis in South Africa that the case has been mentioned.

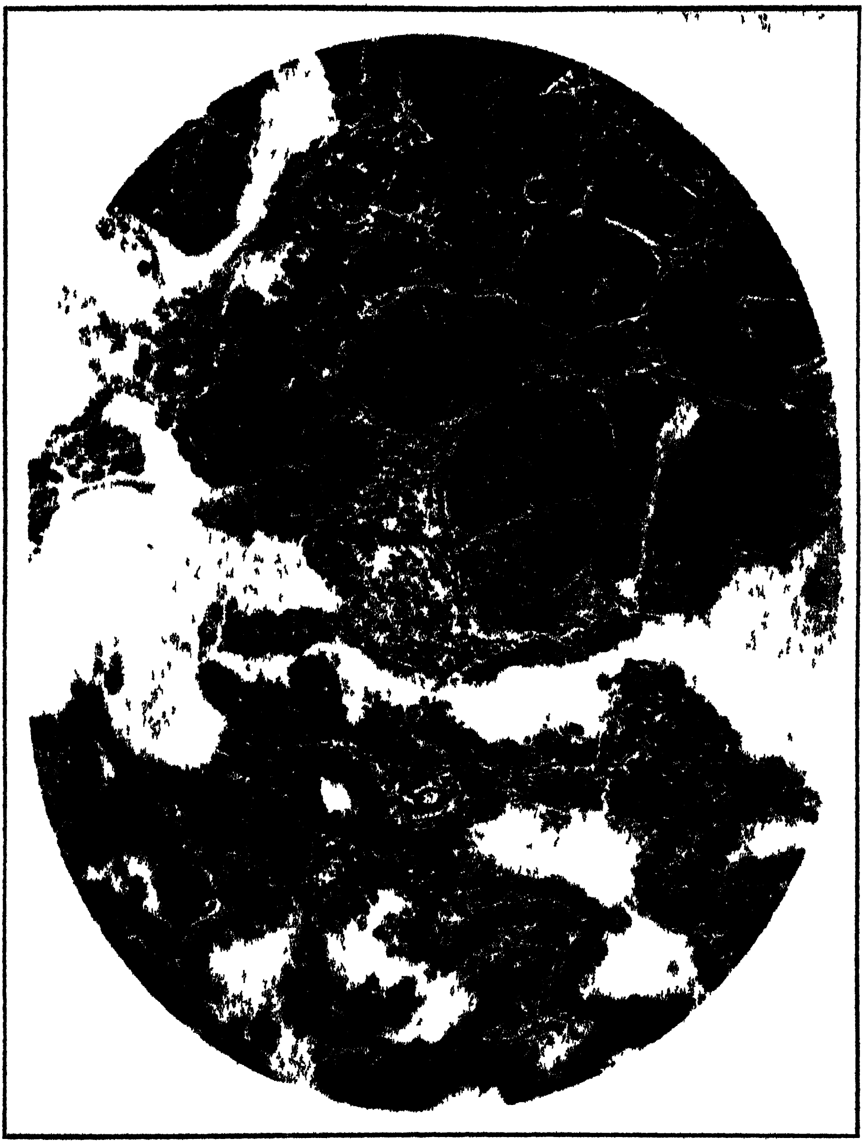

Fig. 59.—Structure of another type of pulmonary carcinoma of the dog Adeno-acanthoma, considered to arise from the pulmonary parenchyma Above, solid or acanthomatous structure with keratinisation, below, adenomatoid growth with lumen-formation. (6631, 190 ×)

Mammary Carcinoma.

Regarding mammary carcinoma, some misapprehension has been caused by authors who have under this name reported acanthomas of the skin covering the udder. Yet true mammary cancer cannot be regarded as a rare disease among domestic animals. It is reported to be especially frequent among dogs and less frequent in horses, while in the bovine it must be regarded as exceedingly rare. If from the mammary carcinomas one excludes the mixed tumours of the breast of dogs, however, it is probable that the disease is somewhat less frequent than is indicated in the literature. In equines I find reports of the disease only as affecting the horse. It is of interest, therefore, briefly to place on record here a case in a mule (8099). The indurated udder was thought to be affected by botriomycosis and radical excision was performed, including the regional lymph-nodes; histologically the structure was that of *carcinoma simplex*—a highly anaplastic epithelial tumour without lumen-formation. There was metastasis to the regional glands. The animal was discharged with a healed operation wound two months after excision, but the further history is not obtainable.

In view of the well-known facts regarding the incidence of cancer of the breast in woman, indicating that lactation is far from an essential influence in the aetiology of the disease, and that, on the other hand, in the species with the most highly functional (and abused) mammary gland, viz. the cow, udder carcinoma is rarer than in any other species, the occurrence of cancer in the mule's udder, which has no demands whatever made upon it, is by no means surprising.

Carcinoma of the Testicle.

Malignant "seminoma" is not to be considered a rarity in domestic animals, but in the dog it is less common than benign "seminoma" or adenoma. Schlegel's (1916) review contains much valuable information on this subject, but unfortunately his microscopic observations are given in scant detail and no photomicrographs accompany the descriptions. Fig. 60 is here reproduced to show the structure of the only case which I encountered. The tumour occupied the whole of the testicle of a six-year-old dog, only the epididymis remaining and the thickened albuginea serving as a capsule. Microscopically, one sees small alveoli of cells demarcated by delicate connective-tissue septa. These alveoli are extremely variable in size, being sometimes represented by a strand only one cell in thickness, but usually they measure some 75μ in diameter. They are composed of polygonal cells which may measure as much as 30μ in diameter (but are often also considerably smaller) and which are characterised by their large amount of cytoplasm; this is usually densely crowded with small fatty vacuoles and has a cloudy appearance; in some of the cells (probably degenerate elements) it stains a dense opaque mauve with haemalum-eosin. The nucleus is usually central and varies in shape from spherical to somewhat ovoid; occasionally it is double. The average nuclear diameter is *ca.* 15μ, but the size is variable. There is a sharply delineated nuclear membrane and a finely divided, granular, and evenly distributed chromatin. The nucleoli are one, two, or occasionally three in number and moderately to markedly eccentric. The n : N ratio is usually 1 : 25. Occasional thick strands of connective tissue course through the tumour; they carry the larger blood-vessels and are often invaded by the neoplastic cells. The mitotic index is 2.

The tumour described seems to correspond with Schlegel's *carcinoma medullare*, which he indicates is the most frequent type of primary carcinoma of the testicle. In the human pathology the classification of testicular tumours is a matter of great difficulty and considerable controversy. It would appear that this tumour of the dog corresponds with the embryonal carcinoma (Ewing) or seminoma (Chevassu, 1906) of man and one is certainly impressed by the embryonal character of its cells. Ewing considers such tumours to be one-sided developments of mixed neoplasms, but until such time as further studies may be made of the histogenesis of these tumours in animals, the accepted classification of the veterinary literature will serve.

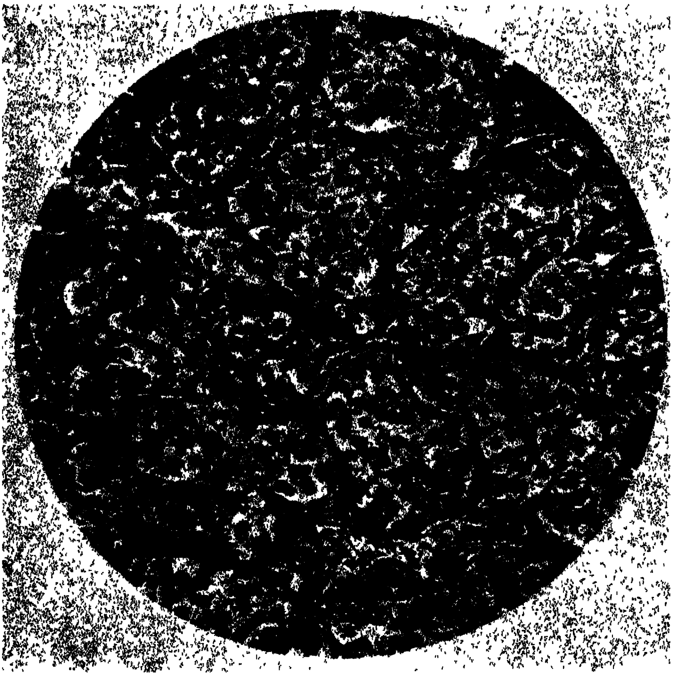

Fig. 60.—Structure of carcinoma of the testicle (seminoma) in the dog. (14319 ; 200 ×).

Transitional Cell Carcinomas of the Ox.

Carcinomas classed by Ewing as transitional cell carcinomas were found four times; all cases affected bovines and the site in two cases was the nasopharynx and the ethmoidal mucosa respectively while in the remaining cases only the secondary glandular lesions were submitted(⁸). Tumours of the mucosa of the ethmoturbinates of bovines are best known in Sweden, in which country, according to Sternström (1915) and Magnusson (1916), they occur with striking frequency and apparently in endemic form. They are also seen in that country in horses, although less frequently. According to Magnusson, who made a careful histological study of these interesting and apparently(!) contagious tumours their nature varies from carcinoma or adenocarcinoma to sarcoma, and mixed tumours of these two entities occur. He indicates further that on the same farm, the tumours, or at least the majority of them, have a similar histology. The fact that tumours of a similar nature occur in this country is worth record. Only one case is here reported, but since this was obtained another has come into my possession. In this second case (which is not here recorded) recognising the nature of the growth I inquired whether other animals in the same byre were similarly affected and found that two cows in one byre had at the same time shown similar symptoms. It thus appears that as regards not only the pathology but also the epidemiology of these tumours we have probably here to deal with the same phenomenon as has been reported by the Swedish authors. Doubtless more cases would come to notice if practising veterinarians were aware of the almost pathognomic significance for this disease of the following syndrome in bovines: deformity of the face due to swelling of the frontal and maxillary regions (i.e. the region of the paranasal sinuses), dyspnoea, discharge of blood and pus from the nostrils, unilateral exopthalmos, and often (later) swelling of the pharyngeal lymph-nodes and nervous symptoms (" madness "). The first case of this disease which came to our notice is reported here (from Pietermaritzburg), the second two cases occurred in Johannesburg.

(*Bovine*, 16245.)

The subject was a Fries cow, 12 years of age which was destroyed owing to a disease of the head(⁹). At post mortem a marked hard swelling of the right side of the head was seen, extending from the base of the horn to the lower limit of the maxillary sinus. There was a defect (ulceration) in the region of the right supraorbital process. Marked right-sided exopthalmos was present and the conjunctival sac was filled with pus. The bones at the base of the horns and over the frontal and maxillary sinuses were soft (easily cut with a knife). The frontal and maxillary sinuses were distended with fluid. The specimen sent in consists of the orbital region and the neighbouring parts of the right side, from which the skin has been removed. The eye not only protrudes markedly (exopthalmus) but is displaced owing to pressure from the postero-superior aspect of the eye-ball. The external aspect of the cheek region bulges outwards and the bones are covered by a thick layer of firm white fibrous tissue (*periostitis fibrosa*) and are softer than normal (*osteitis fibrosa*). On

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(⁸) It is possible that in other cases diagnosed as secondary carcinomas transitional cell tumours were concerned. Although in the two cases mentioned above it was possible to recognise the variety of carcinoma, one cannot be certain that with increasing anaplasia this might always be the case.

(⁹) I am indebted to Mr. Paine, M.R.C.V.S., and to Mr. Osrin, B.V.Sc., of the Allerton Laboratory for many details of this case.

its internal aspect the specimen shows a large tumour mass medial to the orbit and occupying also the frontal sinus and the orbit. The medial (bony) wall of the orbit is perforated and the mass continues from the sinus to the internal aspect of the *bulbus oculi*, which is rotated upwards and backwards owing to the pressure, so that the pupil lies close to the dorsal margin of the orbit. The tumour tissue is yellowish-white and firm, almost fibrous, in consistence. Medially it has a cut surface which would have been in close proximity to the ethmoid bone; and on inquiry from Mr. Osrin, who had performed the autopsy, he agreed that the disease had apparently commenced in the ethmoidal mucosa. The aboral portion of the maxillary sinus is present and shows the presence of fungating growths of diffuse distribution replacing the mucosa. These tumour masses are of a softer consistence than the first-described mass.

Microscopically the tumour tissue is seen to consist of a variable and often very large amount of connective-tissue stroma, which for the most part is richly cellular, forming bundles of proliferating fibroblasts with collagenous tissue which course in various directions and support aggregations of epithelial cells which are usually arranged in elongated branching strands two or more cells in thickness. Some of these cell-strands show lumina filled with degenerated cells. The cells often show a tendency to some preservation of polarity and are cuboidal in type, but more often there is loss of polarity and absence of a lumen, and the cell-shape is polyhedral. The nuclei tend to be hyperchromatic and the nucleoli, which number two to four, are often considerably more prominent than in normal glandular epithelium. Mitoses are fairly frequent (index=3). In other parts, especially at the growing edge of the tumour mass, where occur spicules of decalcified bone with numerous osteoclasts at their borders, the cells are arranged in more rounded alveoli without lumina and the stroma is less in amount although very richly cellular. The fibroblasts of the stroma show occasional mitotic figures and rather more prominent nucleoli than usual, but the size of the latter is still considered to be within the normal limits for rapidly proliferating connective-tissue elements and therefore the cells of the stroma are not necessarily to be regarded as malignant (e.g. as in a mixed tumour). The cytoplasm of the neoplastic epithelial elements is fairly homogeneous or very faintly granular and is acidophilic; no intercellular spines are seen. Centrally the cells may be irregularly degenerated to form false lumina. Small cysts are present in other parts, imperfectly lined by neoplastic epithelium and containing necrotic neoplastic cells and dense, hyaline, acellular masses reacting strongly with acid fuchsin (collagen); there are also present fragments of the (resorbed) bone. Intermediate stages of decalcified bone surrounded by osteoclasts and lying in epithelial-lined lumina are also to be found. In parts the stroma is hyaline and consists of fibrous tissue whose blood-vessels are surrounded by a mantle of lymphocytes mixed with proliferating fibroblasts. In one part deformity of the veins of the stroma is caused by the pressure of contiguous neoplastic alveoli: the tumour cells may penetrate as far as the intima, reducing the lumen to a small slit; in one case actual vascular invasive growth is seen, a vessel being lined by tumour cells which show a distinct tendency to keratinisation; these cells often have bizarre nuclei and appear much more closely related to squamous than to glandular epithelium. This lining of the vascular lumen is several cells in thickness and only the inner layer shows to a marked degree the changes mentioned, the outer cells somewhat resembling " basal epithelium ". Due to this invasion only the adventitia of the vessel persists; but it has a patent lumen containing (circulating) blood. In the same section showing these changes are to be seen alveoli whose cells have considerable keratinising tendencies: they are polyhedral, squamous-like elements with distinct intercellular boundaries (cuticles) and very prominent acidophile nucleoli. Such alveoli may also be associated with a pronounced lymphocytic infiltration of the contiguous stroma, and appear to be surrounded by a zone of lymphocytes and proliferating fibroblasts.

Remarks.—The post-mortem findings allow one to say beyond reasonable doubt that this tumour had its inception in the ethmoidal mucosa, and both the gross pathology and the histological structure present a close agreement with ethmoidal tumours of bovines described in the literature. Tumours of this histology fall appropriately into the class of transitional cell carcinomas, by which is indicated malignant tumours intermediate in character between glandular carcinomas and acanthomas. In this case the epithelium may be cuboidal in type, lining lumina, or it may undergo keratinisation. The presence of bone in the tumour tissue is a result of the great destruction of pre-existing bone which its advance through the skull occasions. The presence of rapidly proliferating fibroblasts and dense masses of lymphocytes often in intimate relation to the epithelial alveoli is also probably to be interpreted as secondary manifestations in the stroma, not justifying a diagnosis of a mixed neoplasm. One is tempted to question (albeit, on the basis of this one case, diffidently) whether the " carcinosarcomas " of the ethmoidal mucosa which have been reported in Europe should not also be regarded as simple tumours, with marked " round-cell " infiltration and even proliferation in the stroma. This tumour, arising from the ethmoidal mucosa, is most favourably situated to undergo the invasive spread which it accomplishes, viz., into the nasal chamber, the maxillary and frontal sinuses, and the orbit.

Diagnosis.—Transitional cell carcinoma arising in the mucosa of the ethmo-turbinate and invading the paranasal sinuses, the orbit, and the bones of the skull.

CHAPTER IV.

Tumours of Epithelium (Concld.): The Special Problems of Primary Epithelial Neoplasms of the Liver and the Thyroid.

EPITHELIAL TUMOURS OF THE LIVER.

In deference to an almost universal tendency in the literature, which is, in view of the problems involved, a very correct attitude, it is proposed to discuss under this heading all primary epithelial tumours of the liver, whether benign or malignant, together with the tumour-like hyperplasias which characterise the pathology of this organ.

An excellent account of primary liver cell carcinoma is given by Hoogland (1926) who has also summarised all the older literature. Of the latter, perhaps only the observations of Trotter (1904 and 1905) give a detailed description of the gross pathology of a large number of cases while unfortunately the histopathological observations are by no means so closely recorded as could be desired. Hoogland, on the other hand, enters into considerable detail regarding the histological appearances, indeed to a degree but seldom seen in the veterinary literature. It is hoped that the observations made in this paper, although more limited as regards the species distribution, may yet add something of value in the way of more minute descriptions of the cytology of these tumours.

CLASSIFICATION AND NOMENCLATURE.

True primary epithelial tumours of the liver are divided into those arising from the hepatic parenchymal cells and those arising from the intrahepatic bile ducts.(1) In regard to the former group, it is well known from an extensive literature in regard to these diseases as they affect man, that the greatest difficulties and controversies have existed (*a*) in regard to the definition and criteria to be used in the discrimination of actual neoplastic processes from localised hyperplasias of the hepatic tissue, and (*b*) with reference to the definition and discrimination of benign and malignant tumours. It is now fairly universally admitted [see for example the extensive review of Herxheimer (1930)] that no sharp line of distinction can be drawn between nodular hyperplasias, adenomas, and carcinomas, and it is very generally conceded that the one process may be the direct forerunner of the next. This fact does, not, however, absolve us from the duty of discriminating between these three types of proliferation wherever possible and of indicating by a clear terminology, at least in typical cases, which of the three processes is in operation. The tendency of some authors to escape from the dilemma by the use of non-committal terms such as hepatoma([2]) and " malignant adenoma " is therefore to be deprecated, although it is very understandable. It is not to be imagined, because we discriminate hyperplasias, benign tumours, and malignant tumours of liver cells, naming them hyperplasia, adenoma, and carcinoma respectively, that these processes are rigidly distinct or that we are not alive to the extreme difficulty of separating them in many cases. A further confusion in classification arises from the inability to distinguish (in certain species at least) between tumours of liver cells and of bile-duct cells. It is commonly believed that here also no sharp border-line exists, and that intermediate forms occur. This, however, has not been our experience in domestic animals. Lastly it has been common in veterinary pathological diagnosis to report " carcinoma of the liver ", shirking the decision as to whether the lesions are primary or secondary. It is most important to do this in every case, and we have not encountered cases in which, even though only liver was available for examination—and perhaps even but a fragment of the organ, this discrimination presented serious difficulties.

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(1) There is also the question of hypernephromas (tumours of adrenal origin) arising primarily in the liver of man, but not observed in animals.

Great confusion exists more especially in the indiscriminate interchange of the terms adenoma and carcinoma in the literature. In view of the fact that it is generally admitted that, on purely morphological criteria, no universally valid distinction can be made, we here follow Herxheimer in considering this distinction not one dependent on presence or absence of anaplasia, on presence or absence of (especially extrahepatic) metastasis, or on presence or absence of of encapsulation; but purely on the criterion of whether or not an intravascular invasive tendency is present. For the liver-cell tumours at least, this remains our only anchorage in a sea of difficulties. Many of the points outlined here will become clearer as the discussion of the pathology proceeds.

OCCURRENCE.

Considering domestic mammals as a whole, primary liver tumours are among the most frequent of internal epithelial neoplasms. Trotter's (*loc. cit.*) well-known and oft-quoted work in connection with liver carcinoma of bovines need scarcely be mentioned here. His record of 149 cases (as corrected by Hoogland) among 300 bovine tumours gives a clear conception of the great frequency of the disease in bovines, and Hoogland's work also indicates the frequency of primary liver tumours among dogs and cats. Among other animals (sheep, horse) one gathers from the records that primary epithelial liver tumours are less frequent, while for the goat no cases have been described. Regarding birds, Joest and Ernesti (1916) have briefly described 4 cases, in 3 of which they considered the diagnosis of primary hepatocellular carcinoma to be certain.

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(2) There can, however, be no objection to the term hepatoma when used to denote the general group of hepatocellular neoplasms, whether benign or malignant.

I. Hepatocellular Tumours.

A. CARCINOMA HEPATOCELLULARE.

This tumour is encountered most frequently in bovines, all of Trotter's cases and also those described by Hoogland being of the liver cell variety.(³) It is undoubtedly the commonest malignant internal tumour of oxen. It is similarly to be regarded as a common tumour of sheep—(although relatively few cases of neoplasia in this animal have been seen, some 8 certain cases from the literature are mentioned by Hoogland). The tumour has not been recorded with certainty in other domestic mammals (dog, cat, horse) and although primary liver carcinomas have been recorded in the pig by Johne (1899) and Ravenna (1913) it is not known to which variety they belonged, while Feldman (1932) mentions a lesion in the pig diagnosed as " hepatoma, with early carcinomatous changes ". In fowls three cases were described by Joest and Ernesti (1916). In South Africa the incidence of carcinoma hepatocellulare appears to be similar to that in other countries, and in the Onderstepoort collection these growths are encountered most frequently in bovines (5 cases) and ovines (4 cases), while there is one example from the domestic fowl and two from species not stated, one of which was considered possibly to be a dog.

PATHOLOGY.

(i) *Cases in Bovines.*

Case 1 (*Bovine*, 2121).

This tumour was described as being situated in the right lobe of the liver, measuring 24 x 18 cm. and bulging beneath the capsule. On examination of the slices which constitute the museum specimen, the neoplastic tissue is seen to be lighter in colour than the surrounding liver tissue, the fresh specimen having been described as light brownish and glossy in appearance. It is imperfectly encapsulated, there being many outlying nodules (1 to 2 cm. in diameter) in the surrounding tissue. It contains a large central cavity 14 x 6 cm. lined by fibrous tissue and having gelatinous and cheesy necrotic contents. In other parts also there are large areas of softening, apparently composed of fibrin. In parts the tumour shows distinct connective-tissue septa demarcating irregularly rounded areas 3 mm. to 3 cm. in diameter. In other parts the texture is uniform. Penetration of an hepatic vein was described macroscopically.

Microscopically, the tumour is in large part of its circumference situated directly beneath the greatly thickened capsule of the liver, which provides an effective limitation. For the most part, collagenous stroma occurs only as the adventitia of large blood-vessels of both arterial and venous type which course through the neoplastic tissue, and in most parts there is little suggestion of a lobular structure. The parenchyma consists of cords of cells (one or two elements in thickness) which sometimes have an indistinctly radial arrangement in relation to the larger blood-vessels. These trabeculae appear

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(³) Hoogland considered one of his bovine cases as being of mixed type.

in transection as alveoli which not infrequently but not usually show an insignificant central lumen (usually less than 7μ in diameter) around which the cells may be radially arranged.

The cells have an outspoken resemblance to hepatic cells, being polygonal in shape, not very sharply outlined, measuring some 12μ to 15μ in diameter, with dense, finely granular cytoplasm which stains with haemalum-eosin an opaque pink-mauve, and single, central nuclei which vary more in size than do those of the liver cells. These nuclei are of short-oval shape, sometimes with slightly angular outlines, and vary from *ca.* 6μ to 15μ in long diameter, the latter size being exceptional. Like normal hepatic cell nuclei the typical ones show a moderately prominent chromatin network, but many are affected by pycnosis. The nucleoli, of which usually a single central one is visible in each nucleus, are rather prominent, the n : N ratio appearing distinctly increased; n : N ratios of 1 : 9 are encountered frequently, although in the majority of the nuclei the ratio is in the neighbourhood of 1 : 14. The cells show neither fatty changes nor pigmentation. Multinucleate cells are not seen.

The trabeculae formed by these cells are demarcated by a stroma which is exclusively of capillary nature, no collagen but only reticulum fibrils occurring in the intertrabecular areas. Areas of fresh haemorrhage are frequent. There are also large necrotic tracts (composed of necrotic fibrin, encapsulated by connective tissue and sometimes showing a partial calcification) into which fresh haemorrhages have occurred at the periphery. The blood cells in such areas are intimately mixed with free and well-preserved tumour cells. The tumour cell strands can be seen to grow invasively into the walls of the larger veins of the stroma, even abutting on the intima. Actual sites of pentration were not discovered by a search of the sections, but clumps of free tumour cells mixed with the blood in such vessels could frequently be seen, attesting that intravascular pentration had occurred.

In limited parts of the tumour a fairly regular arrangement of branched and highly collagenised connective-tissue trabeculae demarcate large lobules of the parenchyma, which has a more compact appearance due to the capillary stroma being narrower and less conspicuous. Here also the small lumina described previously and the radial arrangement of the tumour cells around them are of regular occurrence, while the nuclei are more regular in size and their nucleoli less conspicuous.

Mitotic figures were not seen.

The liver tissue shows a cirrhosis, chiefly of the perilobular type, but in parts there is also intralobular penetration of the connective tissue cutting up the liver cells into small groups. There is in parts considerable "round cell" infiltration.

Remarks.—This very large tumour has a structure which is that commonly associated with adenoma: anaplastic changes are slight, mitoses are not seen and one is impressed with the orderly arrangement of the cells. Yet the evidence of intravascular penetration, especially associated with the occurrence of secondary nodules in the immediate vicinity, necessitates a diagnosis of malignancy.

Diagnosis.—Carcinoma hepatocellulare.

Case 2 (*Bovine* 3224).

Macroscopically, the specimen consists of a portion of bovine liver, not otherwise visibly altered, but containing a solitary rounded tumour measuring 11 by 8·5 cm. At part of its circumference it bulges directly beneath the capsule of the liver while at other parts, although there are to the naked eye but faint indications of encapsulation, it yet appears clearly offset from the surrounding liver tissue, which is darker in colour. Occasional thin strands of connective tissue course through the neoplasm and these somewhat imperfectly demarcate solid, rounded masses of tumour parenchyma 1 to 5 cm. in diameter. In places there are small haemorrhages (·5 cm. diameter). Parts of the circumference are limited by the walls of hepatic veins, into which there is no visible penetration. Centrally there is a large, dark, opaque (necrotic) area *ca.* 7 cm. in diameter and having a deep red (haemorrhagic) margin. This area is separated from the tumour tissue by connective tissue. Microscopically, a distinct but very thin connective-tissue capsule is seen to enclose the tumour and in it occur many veins of considerable size. The tumour shows only very occasional supporting strands of collagenised connective tissue, most of the collagen being confined to the larger blood-vessels. As in the previous case the neoplastic tissue is composed of trabeculae (usually two cells in thickness) whose cells have an unmistakable resemblance to liver cells: they are polygonal elements somewhat variable in size (10μ to over 20μ in diameter), moderately distinctly outlined, with single, central nuclei similar to those of hepatic cells, but more variable in size and usually considerably larger. The nuclei measure 7·5μ to 10·5μ in diameter, while larger and obviously degenerate ones may reach a diameter of 15μ. These degenerating nuclei are fairly common and show a distinct chromatolysis, the central portion of the nucleus being unstained (i.e. completely dissolved out) or showing a little cloudy granular debris, while the chromatin is segregated at the periphery causing a marked thickening (up to 1·5μ) of the nuclear membrane. Such nuclei often appear like large vacuoles within the cells. The nucleoli are nearly always prominent, n : N ratios of 1 : 9 being commonly encountered, although 1 : 14 represents a more average figure.

Regarding the cytoplasm of the tumour cells, a feature is the variation in staining reaction, not only from one part of the tumour to another and from one cell to the next, but actually within one and the same cell. Thus the cytoplasm may be distinctly eosinophilic or distinctly basophilic. It is not known whether this may not be an artefact due to the long preservation (13 years) in Kaiserling. However, in some sections this variability is not seen and of these it can be said definitely that the cytoplasm is less eosinophilic than that of the liver cells. The cytoplasmic granulations are fine and inconspicuous. Lumina are seldom seen and when they occur are small and ill-defined, no distinct radial arrangement of the cells being seen around them. The cell trabeculae are separated by a stroma exclusively of capillary nature and only moderate in prominence.

In one section evidence of invasion of a capsular vein is seen and this is confirmed by the presence of circulating tumour cells in the portal radicles of the surrounding liver tissue. Apart from this the liver shows no significant changes, and no fatty changes or pigmentation are seen either in the liver or in the tumour parenchyma.

Remarks.—This tumour in its general nature is similar to Case 1, viz., it possesses a more "adenomatous" type of structure and shows little anaplasia. Yet it shows intravascular invasion, although metastases are not set up. It is to be remarked that the sterility of emboli is no criterion of a benign nature; on the contrary, the occurrence of vascular invasion, whatever its results, must be held as the final arbiter of malignancy in liver tumours.

Diagnosis.—Carcinoma hepatocellulare.

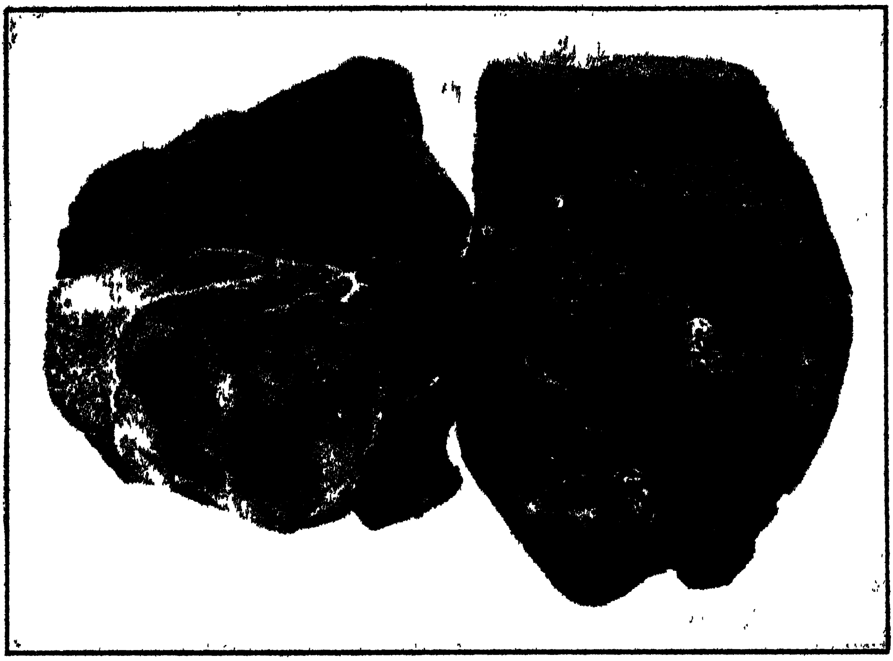

FIG. 61.—Carcinoma hepatocellulare of the ox. (5608; nat. size).

Case 3 (*Bovine*, 5608).

The subject was an aged (16 years) Friesland cow in good condition which was slaughtered on account of sterility. It was stated to have been of senile appearance(⁴). The specimen (Fig. 61) consists of a portion of the liver in which is present a rounded growth 4·5 cm. in diameter, for the most part enclosed within a distinct connective-tissue capsule but at one part of its circumference protruding into the liver tissue, from which however it appears fairly distinctly demarcated. The consistence resembles that of the liver tissue but the colour is much lighter, except in extensive haemorrhagic areas which are present especially towards the centre and which are associated

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(⁴) These details are taken from the work of Quinlan (1929, 15th Report, D.V.S. at p. 927) who investigated the cause of sterility in this animal but was not concerned with the other pathological features.

with strands of connective tissue. In parts a finely lobulated pattern is seen—vaguely demarcated areas 1 to 2 mm. in diameter. The remainder of the liver is not visibly altered.

Microscopically (Figs. 62, 63 and 64) there is in parts a distinct connective-tissue encapsulation (Fig. 62) rich in both arterial and venous blood-vessels. In other parts this capsule is absent and the tumour cells make direct contact with the hepatic parenchyma (Fig. 63). The structure varies somewhat. In general there are elongated columns of cells (usually two cells thick, sometimes more) which have a distinct resemblance to liver cells, being polyhedral and having an opaque granular cytoplasm and somewhat chromatin-poor, rounded to oval nuclei which show a distinct coarse-meshed chromatin network. The following differences between the tumour cells and liver cells are noted: (*a*) they are more variable in size than normal liver cells, measuring between 15μ and 30μ in diameter; (*b*) the cytoplasmic granulations are on the whole a little more distinct, but the liver cells in this material are themselves extremely variable in this respect so that the difference is not constant or striking. The granules are, however, less eosinophilic in the tumour cells than in the liver cells; (*c*) the nuclei are fairly regularly larger, measuring 10·5 to 12μ in long diameter as compared with 7·5 to 9μ for the liver cell nuclei; (*d*) the average nucleoli of the tumour cells bear an areal ratio to the nucleus of 1 : 14 to 1 : 25. (In the liver cells, this ratio is usually greater than 1 : 25.) When it is also remembered that the tumour cell nuclei are enlarged, it will be seen that this implies a marked absolute enlargement of the nucleoli of the neoplastic cells and they are in consequence considerably more prominent than in the liver cells; (*e*) sheaves of needle-like crystals are frequent in and among the tumour cells. They stain very weakly with Sudan III.

The tumour cell columns are separated by a stroma which consists exclusively of capillaries with associated fibrillar reticulum, no collagen being seen. This is a prominent feature. In some parts, however, there are also present trabeculae of loose and open collagenous tissue carrying larger blood-vessels and these may completely or incompletely demarcate lobules of tumour parenchyma of very inconstant size. These lobules appear to correspond roughly with liver lobules, but central veins, bile-ducts, and a radial arrangement of cell trabeculae are absent. This structure occurs only in limited parts of the tumour.

Small lumina, some 9μ (occasionally as much as 15μ) in diameter (Figs. 62 and 63) occur fairly frequently and in transection the cells of the cords are seen to be radially arranged around them. The larger lumina are irregularly bordered by the tumour cells which do not at any time assume an outspoken columnar form. A fair number of shrunken cells with strongly eosinophilic cytoplasm and pycnotic nuclei are seen. Mitoses are absent.

Occasionally, indications of vascular penetration may be seen, and tumour cells occur rarely within the veins of the capsule. In one section it is seen that there has been invasion of a medium-sized vein of a connective-tissue trabecula immediately beneath the capsule: the vessel is lined by tumour cells which assume a more cuboidal form and grow into the vascular lumen as papilliform elevations (Fig. 64).

The liver shows no other pathological alterations and there is no pigmentation either of the liver or of the tumour cells.

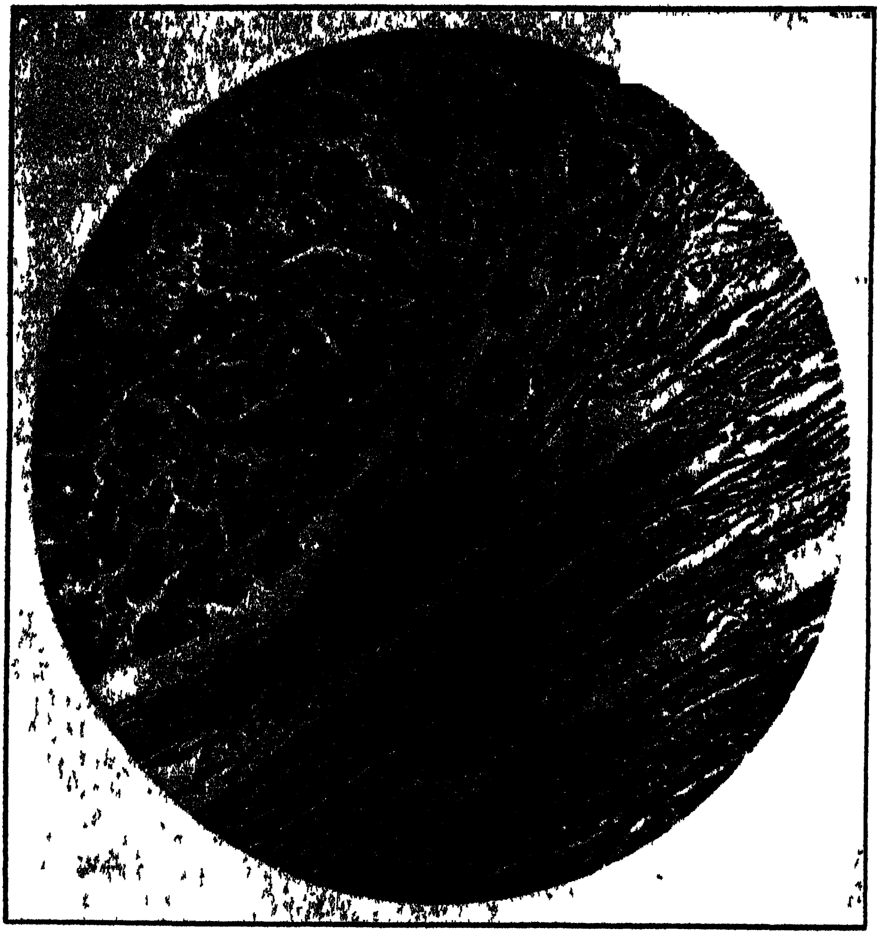

FIG. 62.—Structure of the hepatocellular carcinoma of the ox shown in fig. 61 · Limited anaplasia and strict encapsulation at this portion of the circumference. (5608; 250 ×).

Remarks.—This tumour had previously been diagnosed as "liver-cell adenoma", which is readily understandable when the regular arrangement of the cells, the (at least partial) encapsulation, and the limited anaplasia are considered. The closer analysis undertaken here, especially of parts of the tumour (which had not previously been sectioned) where aggressive growth occurs, renders the

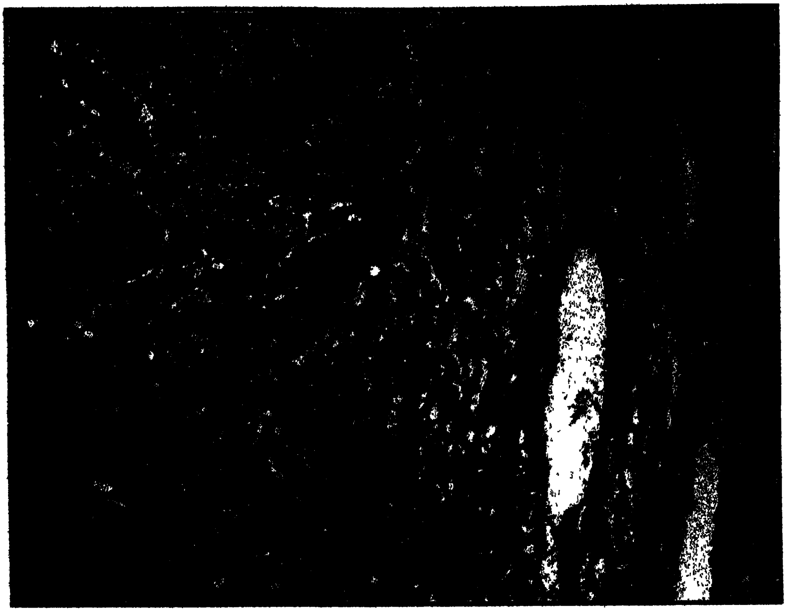

FIG. 63.—Another portion of the margin of the hepatocellular carcinoma shown in fig. 61: Failure of encapsulation and direct encroachment on the hepatic tissue at the right side of the field. (5608; 125 ×).

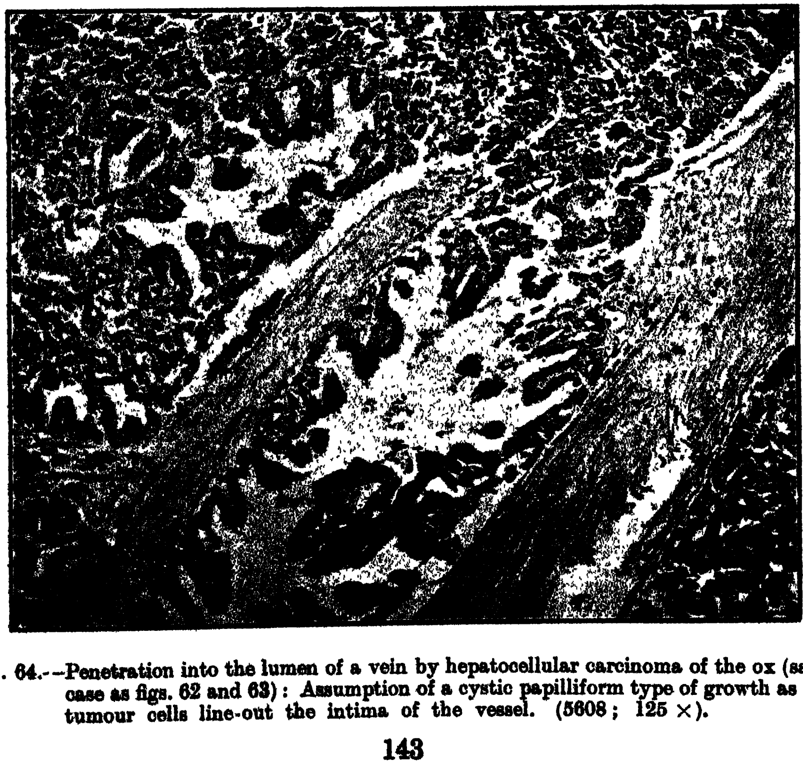

FIG. 64.—Penetration into the lumen of a vein by hepatocellular carcinoma of the ox (same case as figs. 62 and 63): Assumption of a cystic papilliform type of growth as the tumour cells line-out the intima of the vessel. (5608; 125 ×).

above diagnosis untenable according to the criteria we are using; and in spite of the absence of establishment of metastases, their possibility remains and the growth must be considered malignant.

Diagnosis.—Carcinoma hepatocellulare.

Case 4 (*Bovine*, 6072).

This specimen has previously been described by de Kock and Fourie (1928) who kindly gave me permission to undertake a critical re-examination of their material. From their description we learn that the specimen consists of " a piece of bovine liver . . . showing the presence of a circumscribed tumour . . . the tumour is present in the substance of the liver, but at one place it is associated with the capsule and can actually be seen on the surface of the organ. The capsule of the liver, over the neoplasm, stands out as a pale greyish-white area 4 cm. in diameter. Over the tumour the capsule is irregularly thickened and raised above the surface of the liver. In the substance of the liver it (the neoplasm) is found to be circumscribed and sharply marked off from the apparently normal liver tissue by a well-defined fibrous capsule which varies in thickness from ½ cm. to 2 cm. In the latter thick portion there are several foci which vary in size from 1 mm. to 4 mm. in diameter, these foci vary in colour from pale greyish yellow to a pale green. The substance of the neoplasm shows a lobulated appearance. The lobules vary in size from those 2 mm. in diameter to elongated ones 1 cm. long. In between the lobules are reddish spots (haemorrhages) here and there. In places these assume a linear appearance and occur regularly throughout the substance of the neoplasm. The colour is for the most part green, but lighter shades of greyish and even yellowish green can be identified . . . Red spots and sometimes red lines occur in an irregular manner throughout the substance of the tumour ". To this description it should be added that the neoplasm is irregularly rounded in outline, that it measures *ca.* 4 cm. in diameter and that besides the smaller nodules present in the tumour capsule there occur several entirely outside the capsule but in the immediate neighbourhood of the main mass. These are fairly sharply circumscribed but to the naked eye show no sign of encapsulation. There are further multiple foci 1 mm. to 5 mm. in diameter, distinguished from the liver tissue by a lighter colour but not otherwise sharply demarcated therefrom. Further, the capsule appears very deficient if not entirely lacking in places and irregular masses of neoplastic tissue appear here to bud off from the main mass and to lie in immediate contact with the hepatic parenchyma.

Microscopically, in the sections available there is a dense collagenous capsule which completely encloses the greater part of the circumference of the main tumour mass from the surrounding liver tissue, although it varies greatly in thickness. From this capsule occasional trabeculae of collagenous tissue proceed through the substance of the neoplasm. Apart from these and occasional blood-vessels accompanied by a little collagenous tissue, the stroma is entirely of capillary nature and demarcates one from another the parenchymal units to be described. In general this capillary stroma is somewhat more prominent than the corresponding (intralobular) capillaries of the liver tissue. The tumour cells are arranged according to two chief patterns: (*a*) trabeculae, usually two cells in thickness, which very often enclose a small central lumen around which (in transection) the cells are radially arranged. These lumina vary considerably in diameter (from 3μ to 15μ) and are moderately sharply outlined by the apices of the cells which however show no distinct cytoplasmic condensation at the free border; (*b*) solid alveoli, often some 60μ in diameter. There are all transitions between these two types, but usually the one or the other predominates in any one part (or gross lobule) of the tumour and is separated from an area of the opposite pattern by a connective-tissue trabecula.

The cells are of polyhedral shape and whether arranged in trabeculae or in alveoli have an unmistakable resemblance to liver cells. In the trabecular units their cytoplasm inclines distinctly to an acidophilic reaction, staining a pink-mauve with haemalum-eosin, while in the alveolar portions the cell cytoplasm is inclined to basophilia. In both cases it is finely granular. The cells arranged in trabeculae are usually somewhat larger (15μ) than those forming alveoli (11μ).

It is noteworthy that *the nuclei of the tumour cells are less irregular in size and shape than those of the liver cells* in the surrounding hepata parenchyma, actual measurements being: liver cell nuclei *ca.* 4·5μ to 15μ in long diameter, tumour cell nuclei 6μ to 10·5μ, only very rarely 15μ, average 7·5μ; and it is clear that the liver cells in this tissue cannot be used as a basis for comparison with the tumour cells. The tumour cell nuclei show no significant differences in pattern from that of the normal liver cell nucleus, being only moderately chromatic, although a minority of the nuclei show hyperchromasia or pycnosis and a few irregular shrinkage. The nucleoli are not conspicuous, the n : N ratio seldom exceeding 1 : 33. Against this, the liver cells in this specimen often show ratios of 1 : 16 and even as must as 1 : 14.

Fatty vacuoles in the tumour cells are not frequent except in the more central part of the tumour, where they occur in about half of the cells and reach the size of the nucleus. A hyaline degeneration in the form of pink staining (haemalum-eosin), glassy globules in the cell cytoplasm is also seen in these parts. In parts the lining cells of the capillaries are prominently filled with a light olive-green granular pigment and the same pigment is also seen within the cytoplasm of many of the tumour cells, although in smaller amount and not easily detectable except on close examination with an oil immersion objective. Much of the pigment present is undoubtedly bile-pigment, but for a fuller study of the pigments present the original publication of de Kock and Fourie (1928) may be consulted.

Binucleate cells are observed only very occasionally—(in the liver cells, on the other hand, double nuclei are of frequent occurrence). The capsule shows pronounced invasion by the tumour cells, forming nodules some of which undoubtedly represent blood-borne metastases in the capsule, since an endothelial lining to the capsular spaces containing these cell masses could often be clearly distinguished.

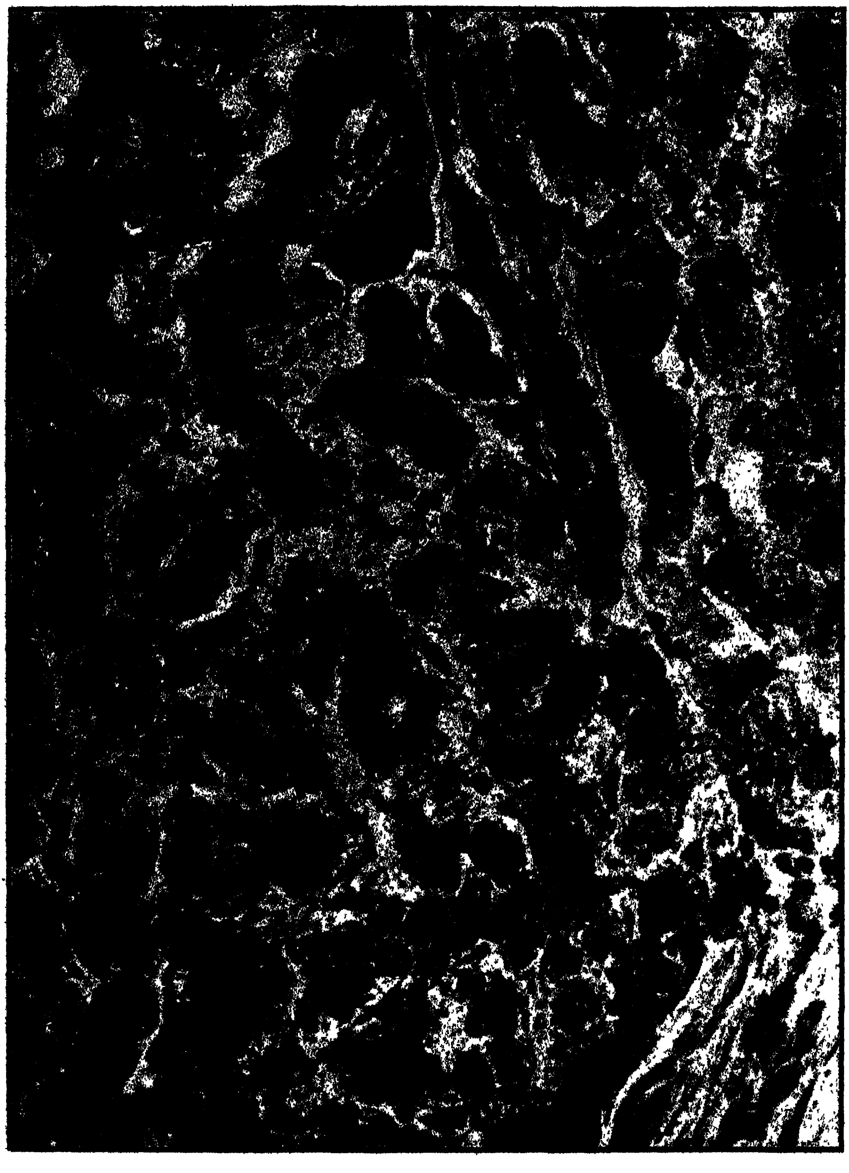

FIG. 65.—Structure of focal hyperplasia (below and to left of centre) in the liver of a bovine which was also affected by hepatocellular carcinoma: The lesion is probably to be regarded as precancerous. Note the signs of anaplasia in the surrounding liver cells (arranged in cords), and their larger and more irregular size as compared with the hyperplastic cells arranged to surround small lumina. (6072; 500 ×).

Outside the capsule, lying within the hepatic parenchyma, are foci of cells in morphology and arrangement identical with the neoplastic cells. These foci (Fig. 65) are, far from being encapsulated, most indifferently circumscribed and to all appearances in direct continuity with the surrounding liver tissue. They disturb the normal lobular arrangement of the liver, being composed of irregular, lumen-containing cell-trabeculae. Their capillary stroma is in continuity with that of the surrounding liver tissue. The cells as well as their nuclei are smaller than those of the contiguous liver tissue and the whole appearance is that associated with a primary focus, contradicting the data one expects to find in the case of a blood-borne metastasis. These foci should be regarded as adenomatoid hyperplasias, although it is likely that they are prospective adenomas and carcinomas.

Within the tumour occur wide endothelial-lined blood-spaces, undoubtedly arising as a distension of the capillaries of the stroma. There are also the haemorrhages described by de Kock and Fourie and small areas of total necrosis. The capsule shows " round cell " and eosinophilic infiltration and in the neighbourhood of the infiltrating tumour foci shows also considerable fibroblastic activity. The mitotic index is 1.

Remarks.—Morphologically this tumour, like those previously described, is greatly lacking in signs of anaplasia and has a low mitotic index indicating a slow rate of growth. The " orderliness " of the tumour tissue is here strikingly illustrated by contrast with the actual liver cells which, if occurring in a tumour, would be described as exhibiting considerable anaplasia. Yet the tumour has formed intrahepatic metastases in its neighbourhood and infiltrates its capsule. It must therefore be considered as belonging to the malignant group and the term adenoma used by de Kock and Fourie is therefore not a suitable one by which to describe it. The general " unbalance " of the liver cells in this case and the formation of multiple foci of hyperplasia are interesting features which will be referred to in the general discussion.

Diagnosis.—Carcinoma hepatocellulare; and multiple "adenomatoid " hyperplasia of the liver probably to be regarded as early stages of neoplasia.

Case 5 (*Bovine*, 9729).

The specimen consists of fragments of bovine liver showing multiple foci of lighter colour (greyish) than the liver tissue. The larger ones are visibly encapsulated, the smaller ones not. They vary from 1 mm. to 1·5 cm. in diameter. Some are confluent. In their substance they show pin-point to pin-head-sized reddish areas (blood). On the surface of the liver they cause irregular small elevations of the liver capsule, covered by the serosa. The whole liver was stated to have been affected and to have been enormously enlarged. The periportal lymph-nodes were also described as affected, all other organs being normal.

Microscopically (Fig. 66), one sees multiple foci, some distinctly encapsulated, others intimately infiltrating the hepatic parenchyma. They consist of a purely capillary stroma supporting trabeculae of cells which have an unmistakable similarity to liver cells. These trabeculae lack orderly arrangement and directional pattern. They are most often two cells in thickness, but often also three or four cells in thickness. The cells are polygonal and their outlines as sharp as those of the liver cells. They are of variable size, measuring 7·5 to 15μ in longest diameter; they do not as a whole differ significantly in size from the liver cells, but show more variation in this respect. The nuclei are on an average slightly larger than those of the liver cells. They vary in shape from spherical to short-oval. Their average diameter is 6μ to 7·5μ and there is considerable uniformity of size and shape. The nucleoli, usually single and central, are more prominent than those of the liver cells, n : N ratios of 1 : 9 being frequently encountered, and the ratio is seldom less than 1 : 16. The nucleoli are thus very regularly enlarged. The chromatin pattern of the nuclei in most of the cells does not show significant departures from that of the normal liver cell nucleus, the nuclei being only moderately chromatic. Hyperchromatic nuclei are, however, seen fairly frequently, relatively coarse granules appearing in the nucleus, especially in the zone adjacent to the nuclear membrane. The cytoplasm is finely but distinctly granular, the granules being somewhat more easily visible than those in the liver cells. It is distinctly less eosinophilic than that of the liver cells, but is not basophilic, the colour (with haemalum-eosin staining) being a

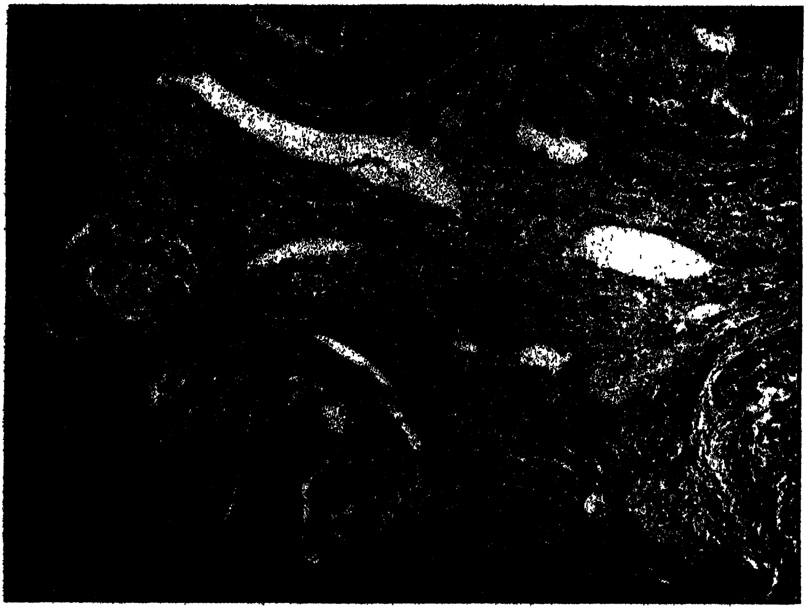

FIG. 66.—A more frankly malignant hepatocellular carcinoma of the bovine: Multiple intrahepatic secondaries invading the liver tissue. (9729; 30 ×).

distinctly pinkish mauve. Small lumina are frequently seen, with the cells somewhat radially arranged around them ("rosettes"). Larger lumina may also be seen distended with serous (pink staining with haemalum-eosin) globules which may cause a distinct concavity of the distal borders of the enclosing cells, or the cells may even be somewhat flattened or cuboidal in shape in consequence of the pressure. These larger lumina may often have quite distinct outlines and the enclosing cell borders appear as a thin sharp refractile line. They often measure 35μ in diameter. Small haemorrhages occur frequently in the neoplastic tissue. Fatty changes are quite insignificant, but a fair number of needle-like crystals arranged in sheaves are to be seen. They stain very weakly with Sudan III and often lie apparently within the cytoplasm of the tumour cells. Finely granular bile pigment (green) may be seen within the tumour cells under close scrutiny with highest magnification but is not a striking feature.

Many of the foci appear to lie within pre-formed spaces and in some of the smaller ones an endothelial lining can be detected showing that the multiple nature of the tumour is to be ascribed largely, if not entirely, to intrahepatic metastasis. Distinct growth of the tumour elements within the portal veins in Glisson's capsule can also be seen. The mitotic index is 2.

The intervening liver tissue is often much compressed. It shows a perilobular cirrhosis and bile-duct proliferation is also to be seen. Fatty crystals may be found among the liver cells and bile-pigmentation is also present. The *Berlinerblau* staining is negative for both tumour and liver tissue.

Remarks.—The clearly invasive growth of this tumour, responsible for its occurrence as multiple foci, as well as the reported metastasis to the regional nodes, leaves no doubt as to the malignant nature of this tumour. Yet in morphology it shows no distinct differences from the non-metastasising tumours with which we have already dealt.

Diagnosis.—Carcinoma hepatocellulare.

Summary of the Pathology of Carcinoma hepatocellulare in Bovines.

The five cases described illustrate the fact that among the cases of bovine hepatocellular carcinoma in this collection there is scarcely one that in its histopathology fulfils the criteria by which frank carcinomas are usually characterised, and it is readily understandable that in two of the cases a diagnosis of adenoma had previously been made. The main lesson to be learned from the microscopic study is that there are no universally applicable morphological criteria by which the malignant cell (in the sense of a cell capable of invasion and therefore at least potentially capable of metastasis) can be recognised. No minute differences are observed between the cells of carcinoma and the cells of (non-invasive and non-metastasising) adenoma. In one case especially, the tumour cells are actually less irregular in morphology than the (as yet) non-neoplastic liver cells. However, there is no doubt that morphological criteria can be of great assistance in adding to the certainty of the knowledge

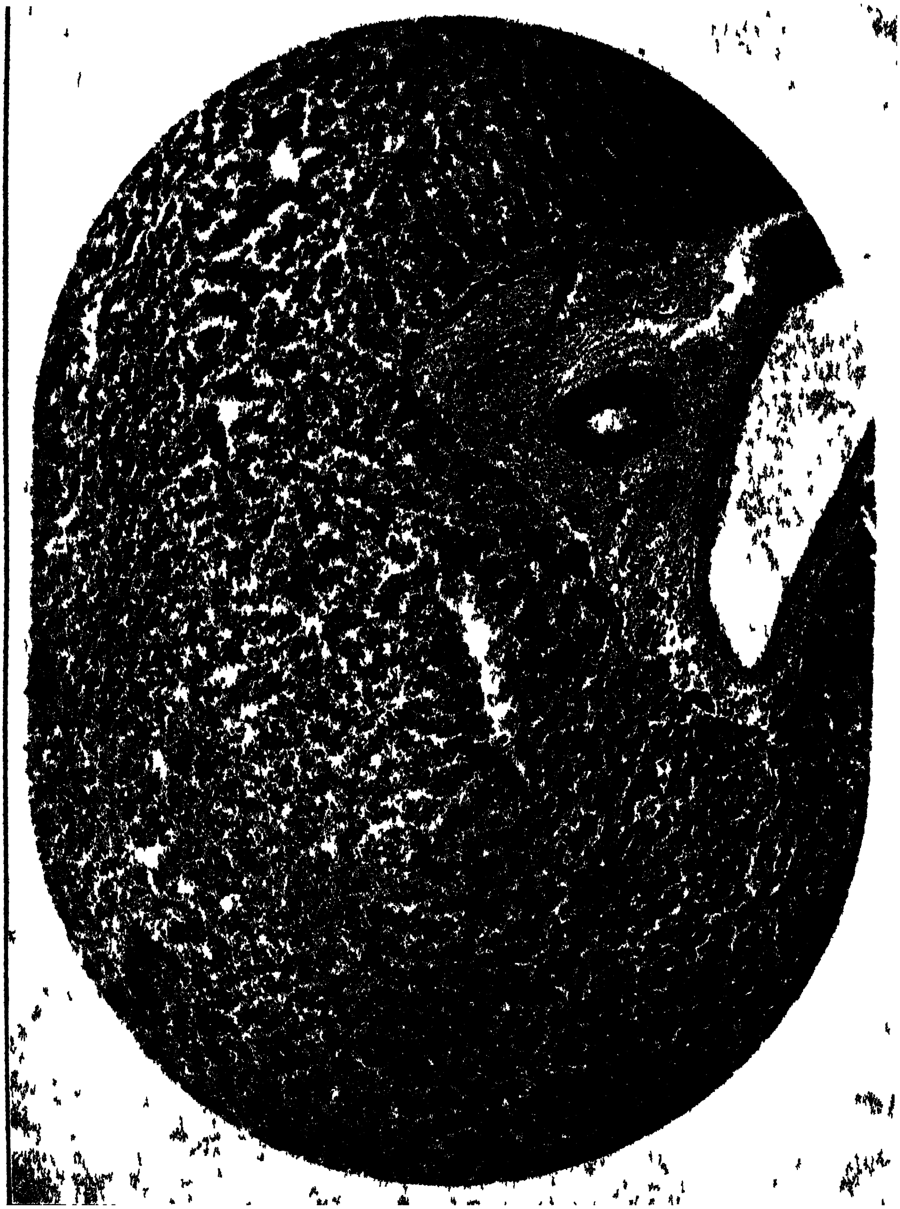

FIG 67.—Margin of an hepatocellular carcinoma of the sheep Above, right, limitation by the connective tissue of a portal tract; below, right, direct invasion of the hepatic tissue. (13043, 120 ×).

regarding exactly what type of lesion one is dealing with, even though not of regular occurrence. In liver pathology it is as well to rid oneself of the commonly accepted conception, of the constancy of the morphological accompaniments of malignancy, for most of them are not applicable. Thus we see that encapsulation, which is partially or fully present in every one of the above tumours is no prerogative of the benign growth. Regarding the cytology, a fairly constant feature is the presence of a greater irregularity in cell size than is found in the normal liver tissue, but it must be remembered that, as illustrated by Case 4, this does not imply that the cells of carcinoma are more irregular in size than *abnormal* but non-neoplastic liver cells. This irregularity is not constantly in the direction of enlargement, although larger cells than in normal liver tissue (e.g. 30μ) may be encountered in some tumours. The size-changes affecting nuclei are more constant and usually the tumour cell nuclei are larger than those of normal liver tissue; what is more constant is a greater variation in size, although, as shown by Case 4, this may not be so great as in non-neoplastic liver tissue. Generally the cell cytoplasm is more basophilic than that of the normal liver cell, but this also is inconstant and great variability may be found in one and the same tumour. The n : N ratio was clearly increased over the normal in 4 of the 5 cases, in one however, the nucleoli remained inconspicuous while the nucleoli of the surrounding non-neoplastic liver cells often reached the average ratio for the nuclei of malignant neoplastic liver cells (usually in the region of 1 : 14). Bile-pigmentation was present in only few cases, and in only one was it present in sufficient amount to affect the gross appearance of the neoplasm (" *carcinoma viride* "). Small lumina were found in every case, although not always in all parts of the tumour: they appear to occur regularly in the " trabecular " arrangements of the cells and to be absent in the " alveolar " form. They are mostly inconspicuous, but may reach a size of 35μ. They are to be clearly distinguished from the outspoken lumina of the bile-duct tumours to be described later, and the essentially polygonal tumour cells are never outspokenly columnar. A constant characteristic is the almost exclusively capillary nature of the stroma. In many of the tumours this is (apart from occasional vessels) the only type of stroma present and it is to be regarded as one of the most important criteria of the hepatocellular nature of a tumour.

Regarding the gross pathology, there was only one case in which on account of striking multiplicity the tumour would have been recognised macroscopically as clearly malignant. The other cases concerned either solitary, well circumscribed tumours or large tumours with inconspicuous secondary nodules in their vicinity. Such nodules are difficult to distinguish macroscopically from primary hyperplastic foci which were present in one case. No constant relation to cirrhosis was found, indeed the tumours were often found in otherwise perfectly normal livers.

It becomes clear that in the majority of cases of this tumour in bovines a close microscopic study of sections from several different parts of the neoplasm is a *sine qua non* in the correct estimation of malignancy. This must be based on evidence of intravascular invasive growth rather than on any purely morphological criteria.

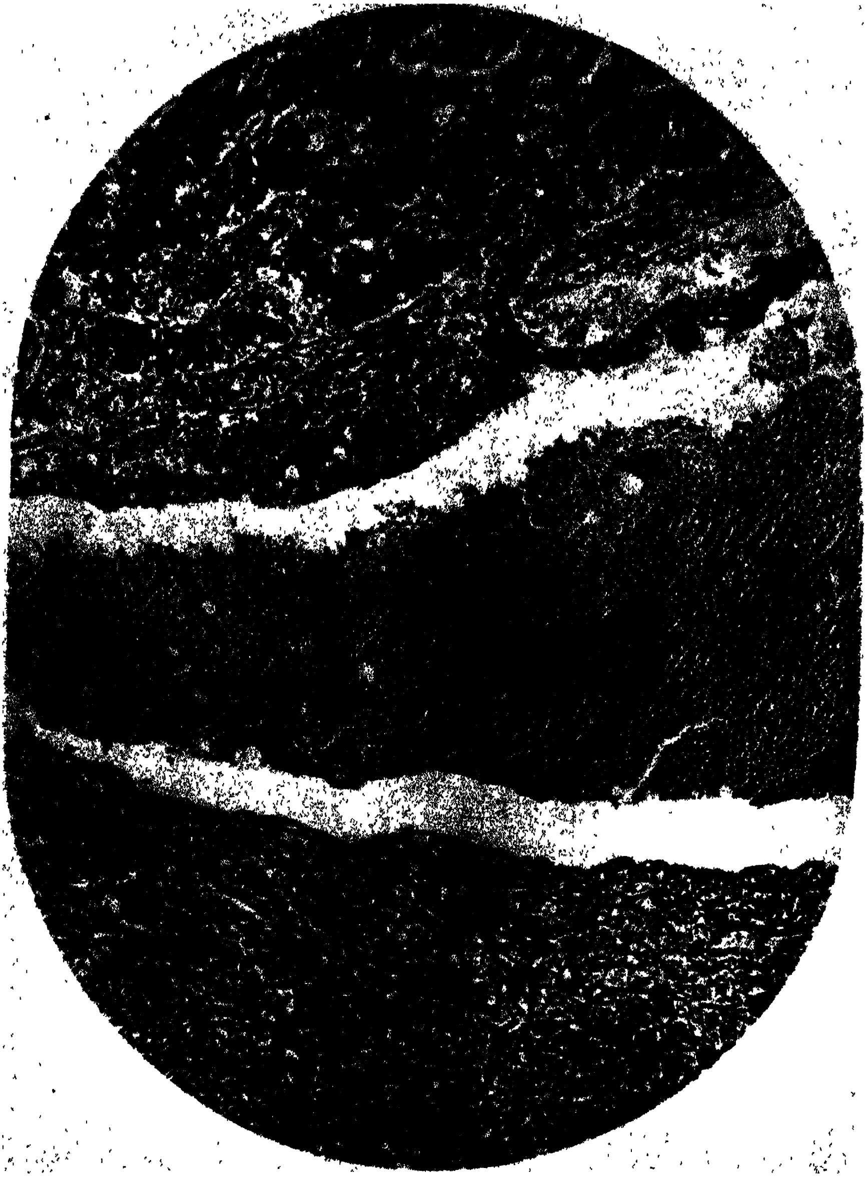

FIG. 68.—A field from the tumour illustrated in fig. 67: Invasive growth into a vein of the stroma and lining of the latter by columnar neoplastic elements; note continuity with the more typical tumour tissue above. (13043; 215 ×).

(ii) *Cases in Ovines.*

Case 6 (*Ovine*, 13043).

Macroscopically this specimen is a portion of ovine liver showing a non-encapsulated and not always distinctly outlined rounded tumour, of which the size cannot be accurately given (it was at least the size of a walnut). It is lighter in colour than the surrounding liver tissue which it appears to infiltrate. There are also portions of lung, showing especially along the ventral border multiple, sharply-outlined, often encapsulated nodules, situated within the pulmonary tissue and causing bulgings beneath the pleura; they vary in size from 1 mm. to 1 cm., the larger ones being encapsulated, the smaller ones not. They have a whitish colour.

Microscopically (Figs. 67, 68, and 69) the liver contains an unencapsulated growth whose margins infiltrate the adjacent parenchyma, although in some places they are limited by the adventitia of veins of the portal system (Fig. 67). A collagenous trabecular stroma is absent, the stroma being formed [apart from occasional thin-walled venous blood-vessels, into which penetration of the tumour occurs and in which free tumour cells can be found (Fig. 68)] by capillaries which intervene between the trabeculae of tumour cells. The latter are arranged in columns two cells in thickness and in these an ill-defined central lumen may or may not be present; it is always small (3 to 7μ) and sometimes scarcely visible (1μ). The cells are radially arranged around it. They are fairly distinctly outlined polyhedral elements with a clear resemblance to hepatic epithelium. They are variable in size (averaging 8 to 10μ but reaching a diameter of 21μ); most of them are thus smaller than the liver cells, but the larger ones exceed the diameter of any normal liver cell. The cytoplasm in most parts is faintly to definitely eosinophilic on account of the presence of fine granules and does not differ markedly from the liver cell cytoplasm. But in other parts the cytoplasm may be definitely basophilic. The nuclei are central, usually single but quite often double, of short-oval shape, and vary from 4·5 to 9μ in diameter, averaging 6μ (i.e. they are not different in size from those of the normal liver cells). Occasionally slight irregularities in outline are seen. The nucleoli are prominent, one or two in number and the n : N ratio is usually between 1 : 16 and 1 : 32. Occasionally the larger bodies which will be described in greater detail in the following case and which are derived from nucleoli are seen: they have a glassy, unstained appearance and show ratios to the nucleus of 1 : 14 (actual diameter may be 3·4μ). Two of such bodies may be present within the nucleus. The nuclear pattern is moderately chromatic in type, and in most nuclei identical with that of the liver cells, i.e. reticular disposition of the chromatin. Some cells show moderate hyperchromatosis of the nuclei, the chromatin becoming granular. In some parts of the tumour are seen small haemorrhages, small focal lymphocytic infiltrations, and also limited areas of fibrosis of the stroma. It is not seldom that the tumour cell trabeculae have a radial arrangement around a small vein, thus recalling the structure of the liver lobule. Mitoses are sparse, the index being 1.

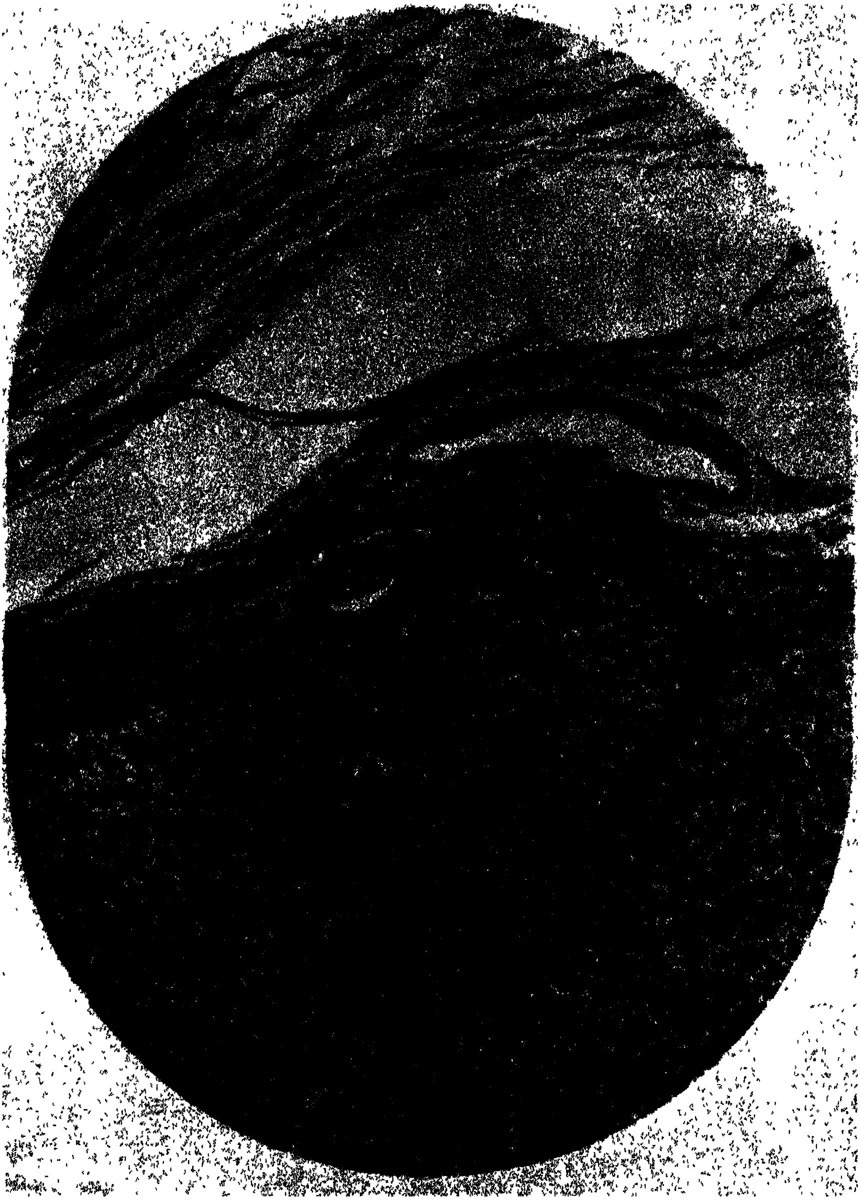

FIG. 69.—Pulmonary metastasis of the ovine hepatocellular carcinoma (shown in figs. 67 and 68): Invasive growth into a bronchiole; round cell infiltration; above, the neighbouring lung tissue. (13043; 100 ×).

In parts there are occasional giant cells, not occurring in clumps but found several in close vicinity to one another. They are irregular in outline, measure up to 37μ in diameter and have a massive, heavily chromatic (granular) nucleus, which may be twisted, or lobed, or irregularly quadrilateral, and does not show visible nucleoli.

The liver tissue shows moderate fatty degeneration, central to midzonal in distribution, and not affecting every lobule. In the tumour also the fatty changes are patchy in distribution, affecting a minority of the cell trabeculae. But sheaves of crystals, reacting very weakly with Sudan III, are of constant occurrence throughout both the liver and the tumour. The liver cells show a moderate granular bile-pigmentation, which is less pronounced although detectable in many of the tumour cells. There is no haemosiderosis.

Sections of the lung (Fig. 69) show that the metastatic nodules do not differ in essentials from the primary tumour. The larger ones are fully encapsulated, the smaller ones not, although they remain circumscribed. Enlarged nuclei are somewhat more frequent in the lung nodules and the uninuclear tumour-giant-cells described occur often (they were mistaken for megakaryocytes in the routine examination). Lumen-formation is not prominent. Small haemorrhages and lymphocytic infiltrations occur regularly. Intranuclear inclusion of nucleolar origin occur more frequently and may reach a diameter of 6μ. They are hyaline, scarcely stained, and transparent. Their areal ratio to the nucleus may be 1 : 2. The cell cytoplasm is inclined uniformly to a basophilic reaction. In general the signs of anaplasia are more prominent, irregularities of nuclear size and shape, binucleate cells and even multinucleate cells (4-6) being seen more frequently and nuclear hyperchromasia occurring more often. Bronchioles enclosed within the tumour nodules may resist invasion, but in other cases penetration of their walls is seen to be in process (Fig. 69), the neoplastic cells having reached the bronchial epithelium or actually having penetrated into the lumen. Mitoses are absent and were not disclosed by a prolonged search.

Remarks.—This is a tumour of limited anaplasia showing invasive growth and establishment of blood-borne pulmonary metastases, which tend to become (unlike the primary tumour) encapsulated as they increase in size.

Diagnosis.—Carcinoma hepatocellulare with pulmonary metastases.

Case 7 (*Ovine*, 13320).

This is a portion of sheep's liver originating from the Germiston Abattoirs(⁵) and containing a large, solitary, oval tumour measuring 8 by 10 cm., lighter in colour than the surrounding hepatic tissue. A large part of its circumference lies immediately beneath the capsule of the liver, where, although producing slight irregularities of the surface, it is covered by the serosa. At the margin, many vessels of venous type are seen in the thin connective-tissue capsule.

(⁵) The Institute is indebted to Mr. J. Chalmers, M.R.C.V.S. for this specimen.

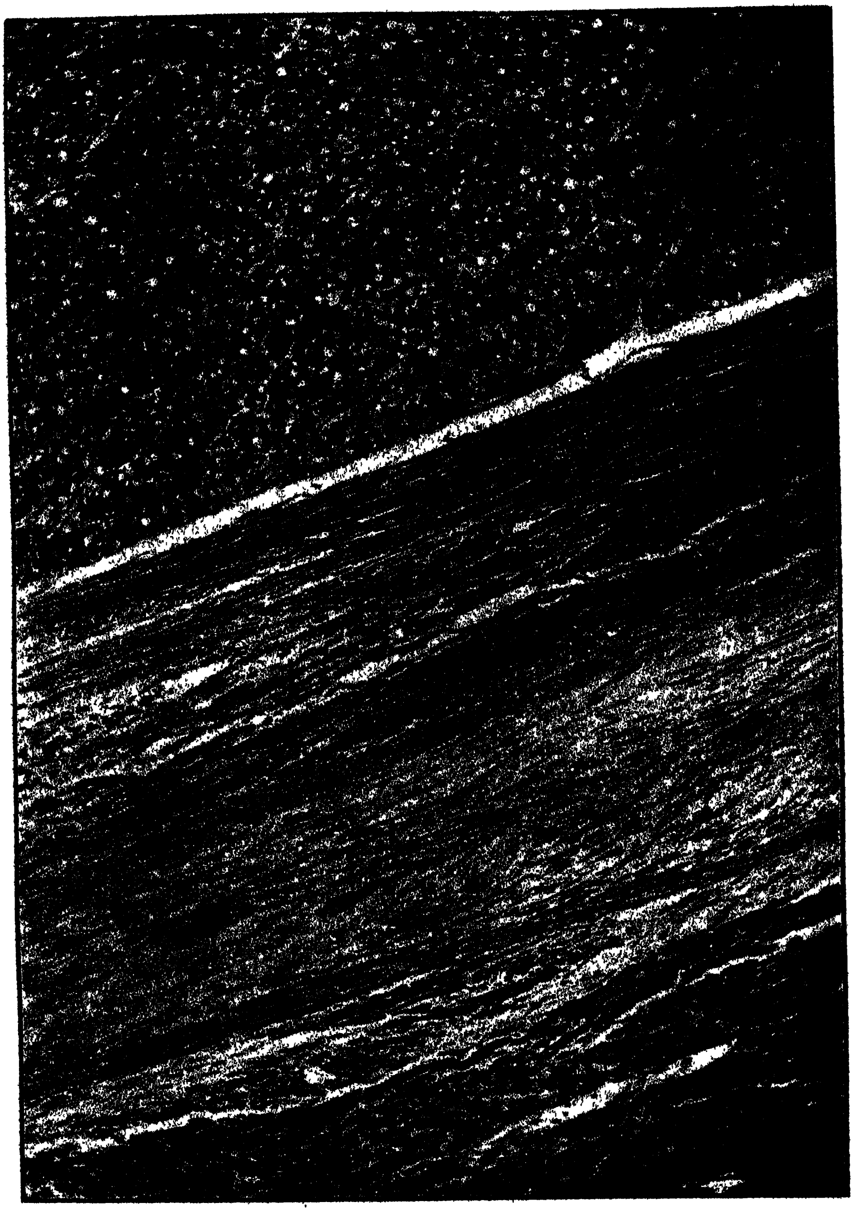

FIG. 70.—Margin of an hepatocellular carcinoma of the sheep: Note fatty changes in the neoplastic parenchyma, and the thick encapsulation against the normal liver tissue (below). (13320; 120 ×).

Microscopically (Figs. 70 and also 10) there is seen to be a thin connective-tissue capsule enclosing the tumour, which consists of trabeculae, two to five cells in thickness, of elements having a distinct resemblance to hepatic cells and which are demarcated by a capillary stroma in which no collagen is present. Very occasional larger blood-vessels of both arterial and venous type course through the tumour. The tumour cells in large parts show pronounced fatty changes and in at least half of them the cytoplasm is almost completely occupied by a single large fat globule which displaces the nucleus to the periphery and causes it to assume a crescentic deformity in adaptation to the pressure. The cells are polygonal in shape, somewhat more variable in size (21 to 28μ) than the liver-cells, but cannot be said to be regularly enlarged as compared with the latter. Individual giant cells occur and will be described later. The nuclei are however usually definitely larger in size than those of the liver-cells (which are *ca.* 7·5μ in long diameter), many measuring 10 to 15μ. The cytoplasm is finely granular and in staining and texture shows no noticeable differences from normal liver-cell cytoplasm. The nuclei are of the same shape (short-oval or rounded) as those of the liver-cells, which they resemble closely except that they tend to be less richly chromatic and therefore usually stain somewhat more lightly. One, two, or three nucleoli are usually visible in each nucleus. Of these, those that are, on account of the typical nucleolar staining reaction, readily identifiable as nucleoli are not all prominent structures although a great many of them are enlarged and n : N ratios varying from 1 : 9 to 1 : 16 are often encountered (cf. the normal, not exceeding 1 : 30 or at most 1 : 20).

Within the nuclei of a number of the tumour cells are also present bodies which may be described as inclusions, but which apparently are derived from nucleoli (Fig. 10). They are rounded, take on no stain, and are perfectly transparent, the nuclear chromatin on the side of them remote from the eye of the observer being clearly visible on focussing to a lower plane of the section. They are sharply outlined by a fine membrane apparently derived from the surrounding chromatoid material of the nucleus and thus in section appear as delicate rings. They may be situated centrally or in contact with the nuclear membrane, and may also lie in contact with a nucleolus of ordinary staining qualities. They vary greatly in diameter—from that of the nucleoli (viz. 2 or 3μ) to over 7·5μ. Two or even three may be present within one nucleus. They may bear a (sectional) areal ratio to the nucleus of as much as 1 : 2·7, in other words may occupy between one-half and one-third of the (sectional) area of the latter. They are by no means especially associated with cells showing either nuclear or cytoplasmic changes indicative of degeneration. Transitional forms between typical nucleoli and these inclusion bodies are easily to be found (i.e. there are nucleoli which stain lighter than the normal brownish-violet shade, especially in their centres) and for this reason they are considered to represent vacuolated or hyalinised nucleoli; their areal relation to the nucleus should therefore come into consideration in the estimation of the n : N ratio.

In parts, giant cells measuring up to 57μ in diameter occur in small clumps. These, on account of their cytoplasmic and nuclear characteristics are obviously derived from tumour cells ("true tumour giant cells "). They had in the routine diagnosis been mistakenly called megakaryocytes: they may have a single much enlarged and lobed nucleus or multiple (e.g. half-a-dozen) separate but closely crowded nuclei; the nuclei often show degenerative changes (hyperchromatosis, pycnosis). On the other hand their nuclei may be even smaller (e.g. 3μ) than those of the other tumour cells and may lie widely scattered in the cytoplasm.

There is in many parts a considerable leucostasis within the capillaries of the stroma; the cells concerned are small lymphocytes and to a lesser extent neutrophiles. Such stasis is not seen in the surrounding liver tissue, which beyond compression in the immediate vicinity of the tumour shows no alterations. In one section is seen massive growth of the tumour tissue within a large vein at the periphery of the capsule, clearly showing the invasive nature of the tumour growth. Outspoken lumen-formation is not seen, but it is common for the cells forming the trabeculae to have a somewhat radial arrangement around a small and indistinctly bordered lumen, usually not exceeding 3μ in diameter. There is no haemosiderosis or bile-pigmentation. The liver tissue shows only slight fatty changes. The mitotic index is 4.

Remarks.—This is a solitary encapsulated tumour whose cells resemble liver cells both in morphology and in relation to a capillary stroma, but have enlarged nuclei and increased n : N ratio, with vacuolation of the nucleoli to form a type of intranuclear inclusion, and which show marked fatty changes. Small lumina are formed sparsely and in parts there is formation of tumour giant cells. Rapid growth is attested by the comparatively high mitotic index and the malignant nature is, in spite of the absence of (recorded) metastases, established by the evidence of intravascular growth. The tumour had been, previously, erroneously diagnosed as adenoma.

Diagnosis.—Carcinoma hepatocellulare.

Case 8 (*Ovine*, 16063).

The specimen consists of the liver of a sheep slaughtered at the Pretoria Abattoirs. The renal extremity of the right (dorsal) lobe and the base of the caudate lobe are replaced by a neoplastic mass which is thinly encapsulated from the liver tissue or in other parts covered only by the serosa of the organ. It is roughly oval in shape and measures 9 by 6 cm. Caudally it abuts on the capsule of the kidney and the vena cava, neither of which are invaded, although a lobe of the tumour invaginates the wall of the latter. The subserous surface of the tumour is uneven on account of the spherical lobes, ·5 to 2 cm. in diameter, separated by fibrous trabeculae, of which the tumour is composed. These lobes, on section, are seen to be sharply outlined and to be further subdivided by secondary trabeculae; finally, polygonal lobules, *ca.* 1 mm. in diameter, much resembling those of liver tissue, can be seen, especially with the hand-lens. The tumour tissue has a pinkish-yellow colour, and its consistence (after 24 hours cold storage) is soft and friable. On section, it is seen to be thinly encapsulated against the liver tissue, but one extracapsular nodule, 1·5 cm. in diameter, is present which is very poorly encapsulated although sharply circumscribed. The neoplastic tissue contains many calcareous particles in places.

Microscopically the typical structure of hepatocellular carcinoma is seen, and in places there are direct invasive growth of the hepatic parenchyma and breaking through into veins whose intimas become lined by tumour cells now assuming a cuboidal shape. The neoplastic cells are arranged in solid or in small lumen-containing cords. There is often marked nuclear hyperchromasia, but the n : N ratio is not prominently altered. The mitotic index is 2.

Remarks.—This neoplasm, received in the fresh state, was readily diagnosed by means of a Giemsa-stained smear. The absence of an increased n : N ratio in an obviously malignant tumour is of interest.

Diagnosis.- Carcinoma hepatocellulare.

Comparison of Ovine with Bovine cases of Carcinoma hepatocellulare.

The only significant difference disclosed in the study of the foregoing cases in bovines and sheep is that in the hepatocellular tumours of the latter species in most cases (two out of three) intranuclear inclusion bodies derived from nucleoli are present whereas these have not been observed in the bovine tumours. That such inclusions are, however, not peculiar to the sheep is attested by their occurrence in other bovine tumours (*vide* thymoma and neurofibroma) as well as in other species (e.g. the dog and the fowl). As in the bovine tumours, increase in n : N ratio is common but inconstant. For the rest, the morphology of the ovine tumours, both grossly and microscopically, closely parallels what is found in the ox. In one of the ovine cases extrahepatic (pulmonary) metastases occurred, while in our own material we have found no such case in bovines. It is well known that extrahepatic metastasis of hepatocellular carcinoma is less frequent in bovines than intrahepatic metastasis, although many instances of records both pulmonary and nephric secondaries are mentioned by Trotter (1904) and the same author (1905) records a case of transcoelomic implantation. Apparently, extrahepatic metastasis has not been previously reported for the sheep, except to the periportal lymph nodes (one case of Frenkel's, 1924). True tumour giant cells occurred in two of the cases in sheep, but were not seen in the bovine tumours. Such cells, well known in " hepatoma " of man, are, however, recorded in the literature as occurring in hepatocellular tumours of the ox by Hoogland. It is obvious from a perusal of Hoogland's work that there is a general tendency to consider " hepatomas " of sheep as adenomas unless actual metastasis is demonstrated. The problem here is identical with that encountered in bovines and every tumour giving evidence of even a potential ability to form metastases must be classed as carcinoma.

(iii) *Carcinoma hepatocellulare in other species of Domestic Mammals.*

As has been indicated above, the only other domesticated mammalian species in which this tumour has been recorded is the pig, and even in the case of this animal a doubt exists (*a*) as to the liver-cell nature of the tumour in the cases of Johne (1899) and

Ravenna (1913—publication not generally available) and (*b*) as to the carcinomatous nature in the case of Feldman, which is not clearly indicated. In the domestic carnivores we learn from Hoogland's work that these tumours are unknown. It is therefore unfortunate that in one of our remaining mammalian cases no record of the species concerned exists: it is thought that the animal concerned was most probably a dog, but no certainty exists and case 8 (dog? 9810) will therefore not be described in detail.

(iv) *Carcinoma hepatocellulare in the Domestic Fowl.*

There is only one case of this tumour in the Onderstepoort collection:—

Case 9 (*Fowl*, 15815).

Macroscopically, the specimen(⁶) consists of pieces of opaque, whitish, friable tissue stated to represent portions of a tumour which occupied the whole of one lobe of a fowl's liver.

In the following description constant reference is made to data concerning neoplastic cells which will be unintelligible unless one knows the normal cytology and histology of the fowl's liver. Unfortunately, of these only the most fragmentary and inaccurate descriptions are to be found in the literature. While it is outside the scope of this work to supply such a deficiency, I have had to make use of my own observations in this connection. These are not to be regarded as being of an accuracy greater than is necessary to make the description of the tumour understood.

Microscopically (Fig. 71) under low magnification this neoplastic tissue bears but a vague resemblance to avian hepatic tissue. The latter should not be described (as it is in textbooks) as lacking lobulation: on the contrary the regular arrangement of central veins and portal systems, with (albeit indistinctly) radiating arrangement of the cell cords, appears to offer a close parallel to the structure of mammalian liver, in which however Glisson's capsule is better developed. Yet in respect of distinctness of lobulation I venture to say that there is no greater difference between the liver of the pig and that of the dog than between the liver of the dog and that of the fowl. In this neoplastic tissue there is no lobular structure and collagenous stroma is completely absent, as are also bile-ducts. Irregularly scattered blood-vessels of venular dimensions but lined only by endothelium remind one of central veins. For the rest the stroma is purely capillary in nature and is far less conspicuous than is the normal intralobular system of the avian liver. Further, this stroma, far less distinctly than in the normal liver, separates tubular cords and also more solid masses of cells having a close resemblance to liver cells. The lumen-containing cords predominate and the lumina are far more prominent than in the normal liver, so that an acinous appearance obtains under low magnification; and, if accustomed to mammalian liver tumours only, the observer would at first glance not suspect a tumour of hepatocellular nature.

(⁶) Kindly sent in by Mr. O. T. de Villiers, M.R.C.V.S. of the Stellenbosch-Elsenburg School of Agriculture.

In the normal liver of the fowl the lumina enclosed in the cell cords much resemble those of the mammalian " hepatoma ". They are quite regular in size and inconspicuous, measuring some 1·5μ in diameter, while the cell cords or tubules, in cross-section, may be some 23 to 30μ in diameter. The lumen (as seen in transection) is enclosed by some four to six, most often by five cells. The liver cells are not correctly described as cubical (e.g. Bradley, 1915); their shape is that of a right prism whose faces are squares and whose base is the segment of a circle (a quadrant, or less according to the number of cells surrounding the lumen): this may readily be demonstrated by comparing the outline of the cell as seen in longitudinal section (more or less a square) with that seen in transection of the tubular cord (triangular).

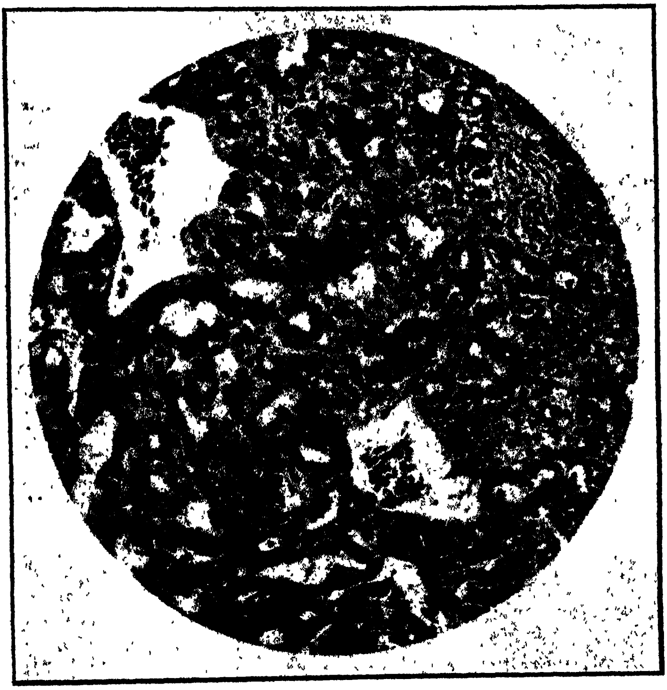

FIG. 71.—Hepatocellular carcinoma in the fowl: Distinct lumen-formation; note polarity of the tumour cells with regard to the walls of veins. (15815; 220 ×).

Compared with this, the neoplastic lumina are seen to be rarely so small as the normal and they are much more variable in size, often reaching a diameter of over 20μ and often enclosed by as many as a dozen cells. The cells are, as is the case with normal hepatic cells, indistinctly outlined. On account of the larger size of the lumina, fewer of them possess the shape of the normal liver cell; such are found bordering only the rarer small lumina. More usually, the larger size of the lumina results in the cells assuming a shape more approaching the cuboidal, or, to be exact, that of a prism whose faces are square and whose base is a portion of a circle-segment which has been truncated along an arc having the same centre as the circle but a lesser radius; or in the case where still larger lumina are enclosed the shape is frankly cuboidal. Polyhedral cells, as in the mammalian liver, occur in the solid cell areas. The cells do not differ notably in size from the normal, but are somewhat more variable, measuring 10 to 15μ in diameter. The cytoplasm while distinctly less acidophilic than normal is yet not basophilic; it is more finely granular than is the normal liver cell. It may be definitely acidophilic in degenerating cells with pycnotic nuclei, which are scattered throughout. The nuclei are single, seldom double, and rarely quadruple, and are much more variable in size than those of the normal liver cells, measuring usually between 6 and 12μ in diameter. They are thus on the whole enlarged, although smaller ones measuring as little as 3μ do occur. The nuclear pattern in a number of the cells does not differ from the normal (sparse chromatic network, but slightly inclined to granularity). However, in most of the nuclei hyperchromasia is a prominent change and they are filled to a variable extent with relatively coarse chromatin granules, while in a number of nuclei there is a diffuse dark staining (pycnosis). The nucleoli are usually single or double and are moderately eccentric in position. They vary considerably in size, the average n : N ratio being *ca.* 1 : 16, but it often reaches 1 : 9. Most are rounded, some slightly oval, angular, or even spindle-shaped. As the normal n : N ratio of liver cells of the fowl varies from 1 : 36 to 1 : 14, it will be seen that the nucleoli in this tumour are enlarged. Further, there occur rather frequently the " intranuclear inclusions " of nucleolar derivation identical with those seen in mammals and described elsewhere in detail. These, when reaching their fullest development, may almost fill the nucleus (areal ratio 1 : 1·5) and are no longer recognisable as nucleoli, taking on no stain. Transitional stages in their development, beginning with a central vacuolation of the nucleolus, are to be found on searching. The bodies often occur in the nucleus along with a " normal " nucleolus.

As mentioned previously, wide blood-vessels having only an endothelial wall are scattered through the tumour. It is usual for the tumour cells in contact with this endothelium to assume a somewhat columnar shape, with their nuclei situated in that portion of the cytoplasm remote from the endothelium (Fig. 71). Evidence of actual penetration of these vessels by the tumour cells was seen occasionally and neoplastic cells may rarely be found free in the vessel lumina; they appeared degenerate. Pigmentation of the tumour cells or of the capillary endothelium was not seen and the lumina are without visible contents. The mitotic index is 1.

Diagnosis.—Carcinoma hepatocellulare.

Remarks on the Pathological Anatomy of Carcinoma hepatocellulare in the Fowl.

The publication of Joest and Ernesti (1916) lacks a minute histological and cytological description of the hepatocellular tumours of the fowl and it seems advisable, even on the basis of this single case, to attempt some comparison with the corresponding tumour of the mammal.

It is worth pointing out the following relations of carcinoma hepatocellulare to adult liver tissue:—In the mammal this tumour tends to assume the pattern of the adult avian or amphibian liver, i.e. the predominant tendency is to the formation of small lumina enclosed by cords of prismatic cells. In the bird, on the other hand, the tumour resembles more the myxinoid liver tissue, viz. it tends to form outspoken lumina enclosed by frankly tubular cords of cells approaching a cuboidal shape. Engaging as this generalisation may at first glance seem, its inevitability becomes apparent when it is remembered that in general there is a tendency for malignant tumours to grow in a pattern similar to that assumed in the embryonic development of the tissue formed by the corresponding normal cells. This fact is of course well known and into it has only too often been read the implication that the essence of the malignant process is a reversion of " adult " cells to " embryonic " cells or even a proof of the development of tumours from " rests " of actual embryonic tissue. Such interpretations are not justified on this evidence alone. It must be remembered that for vigorous cell proliferation a method has already been established in embryonic growth, and that when " adult " cells have an impulse to similarly rapid proliferation it is only to be expected that a similar growth mode will be adopted. As a simile one may recall the theory of recapitulation, whereby we make the generalisation that the evolutionary pattern established in phologeny serves equally well in ontogenetic development. When the biologist, on the basis of the observation of a resemblance between a neoplastic tissue and an embryonic tissue, would postulate an essential identity of the tissues in question, he is guilty of much the same error as the layman, who with a smattering of knowledge of recapitulation, might say that a mammal in its embryonic development is at one stage a fish, at a later stage an amphibian, etc. One should avoid making hasty and superficial deductions from what may be but an economy of natural phenomena. Just as a mode of development which has served successfully in the evolution of species serves equally well in the development of the individual, so there is no need for " Nature " to multiply the mode of proliferation whereby a tissue reaches its normal development in the individual in order to provide a special mode for those proliferations which aim at repair or which constitute neoplasia.

Examining the further details of the histology of these tumours in the fowl, we observe a close general similarity to what has been noted in mammals: the tendency to greater irregularity in cell and especially nuclear size, the latter here again predominantly in the direction of enlargement. An increase in the nucleolar-nuclear ratio is also observed, while it is further seen that the peculiar intranuclear bodies derived from " hypertrophied " nucleoli and found in the mammalian liver and other tumours are not peculiar to the mammal, occurring also in this case of avian hepatocellular tumour. As in mammals also, the almost exclusively capillary nature of the stroma is an important feature in the histopathology.

B. BENIGN PROLIFERATIVE PROCESSES AFFECTING LIVER CELLS: ADENOMA HEPATOCELLULARE AND NODULAR HYPERPLASIAS.

The collection contains four specimens which may conveniently be discussed under this heading. While no rigid separation between adenoma and nodular hyperplasia is possible, yet typical lesions of each may be discriminated and separated. Only one case of solitary adenoma occurs in our material and affects a bovine. The remaining two cases concern pigs.

Case 10 (*Bovine*, 5640).

Macroscopically the specimen (Fig. 72) consists of a slice of liver showing a solitary, large, light greyish mass, contrasting with the surrounding darker liver tissue. It has an irregularly rounded outline and is 13 cms. in diameter. The border is mostly sharp and is often separated from the liver tissue by a small amount of connective tissue in which compressed, slit-like veins are prominent. In other parts a distinct encapsulation is not seen with the naked eye. The tumour shows a fair number of small veins ramifying in its substance and in parts these demarcate small lobules some 4 mm. in diameter.

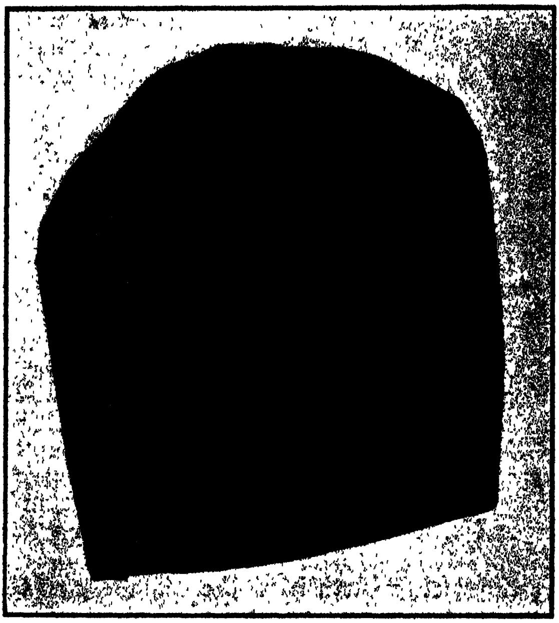

Fig. 72.—Hepatocellular adenoma in the bovine: A well circumscribed lesion showing an expansive type of growth. (5640; 1/2 ×).

In other parts the tissue is diffusely arranged. There are also a few distended thin-walled blood-vessels, some 1 cm. in diameter. Under the liver capsule the tumour produces a low, irregular elevation covered by serosa and forming a visible swelling externally. The remaining liver tissue, save in the immediate vicinity of the growth, where it is compressed, is not visibly altered.

Microscopically the tumour is always demarcated from the surrounding liver tissue, either by a thin connective-tissue capsule containing large blood-vessels or in other parts only by a capillary blood-vessel (without collagenous backing and corresponding to an intralobular capillary of the liver). At no point can invasive growth be seen either into the liver tissue or into the blood-vessels. The tumour cells have an unmistakable resemblance to liver-cells and are arranged in cords, two cells in thickness, having no definite directional disposition. These cords are usually separated by capillaries only; here and there are seen larger vessels which may lie in thin collagenous trabeculae branching inwards from the capsule, and in some parts thin collagenous septa backing the capillaries give an indistinctly lobular structure. The tumour cells are characterised by their considerably greater size than normal liver cells. They are polyhedral or prismatic elements very clearly outlined on account of narrow clefts (artefacts?) between their apposed borders. They often measure 37μ in diameter and few are less than 22μ (the liver cells in the same material averaging *ca.* 15μ in diameter). Their cytoplasm is dense, opaquely staining, eosinophilic and finely granular, showing in fact no significant deviations from that of the liver cells in the same sections. The nuclei are central or often moderately eccentric and are quite frequently double. As regards size and shape they are of a fair degree of uniformity and are mostly spherical to short-oval. A number shows wrinklings or slight irregular projections of the nuclear membrane. They are definitely larger than the liver-cell nuclei, averaging 10·5μ in diameter, while many of them measure 13·5μ, and a few as much as 15μ in long diameter (cf. the liver-cell nuclei in the same section—usually *ca.* 7μ). They are moderately chromatic, showing an open-meshed chromatin network which is often rendered conspicuous by fairly coarse chromatin granules; thus they are slightly more chromatic than the normal nuclei, but no marked difference exists in this respect. The nucleoli appear single or double with about equal frequency, do not appear definitely enlarged (i.e. relatively to the increased size of the nuclei) mostly bearing an areal ratio to the nucleus of 1 : 25, while a ratio of 1 : 14 is only seen exceptionally (cf. the liver cells in the same section, showing ratios of 1 : 14 exceptionally, 1 : 20 more often and usually less than the latter figure). The nucleoli are often not so distinctly outlined as could be wished for purposes of accurate measurement.

An indistinctly radial arrangement of the cells around a minute and indistinct central lumen (1 to 2μ in diameter) is often seen. A few of the nuclei show chromatolysis, their whole central portion being clear, while the nuclear membrane appears thickened and irregular. Mitoses are absent. Pigmentation or typical fatty changes of the tumour cells are not seen, although sheaves of weakly staining fatty crystals occur both in the tumour and in the liver. Apart from this and compression in the vicinity of the tumour and a slight haemosiderosis of the Kupffer cells, the remaining liver is normal; there is no cirrhosis.

Remarks.—A tumour greatly lacking in anaplasia and although incompletely encapsulated showing no power of infiltration or vascular penetration.

Diagnosis.—Adenoma hepatocellulare.

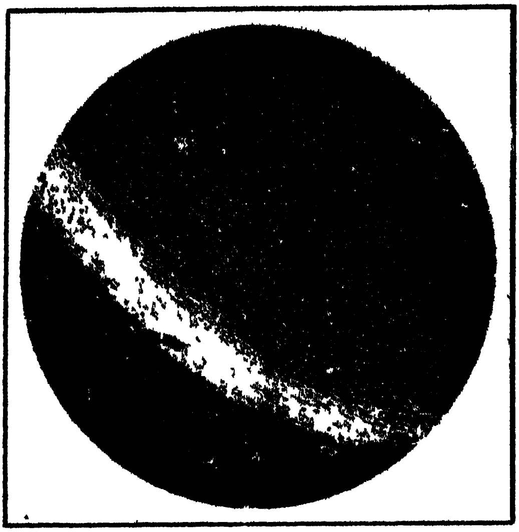

FIG. 73.—Margin of a small hepatocellular adenoma in the pig. Marked encapsulation against the hepatic parenchyma (below). (6454, 33 ×).

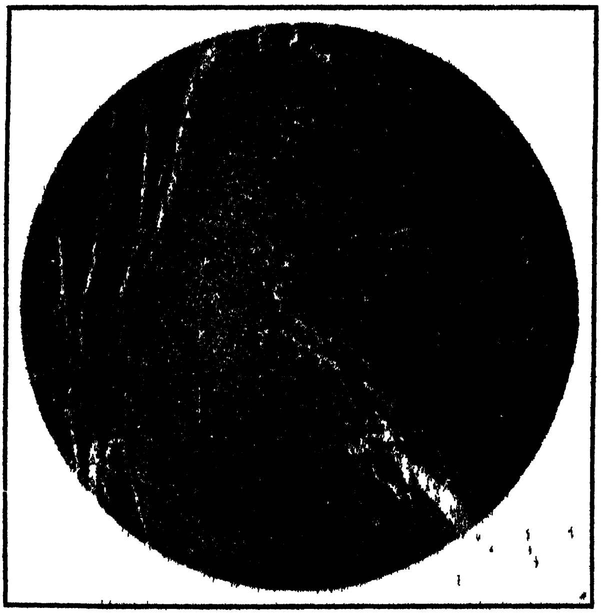

FIG. 74.—Another larger nodule from the liver of the same subject as fig. 73: Circumscription but no distinct encapsulation; pressure atrophy of neighbouring liver tissue (left). (6454; 33 ×).

Case 11 (*Porcine*, 6454).

For macroscopic description there exist only small fragments (remnants of frozen sections) of a pig's liver. These show multiple, circumscribed nodules of rounded outline, lighter in colour than the surrounding liver tissue, and reaching a diameter of 1·3 cm. Most are not visibly encapsulated, but some show encapsulation. They are circumscribed. Further there occur in the liver tissue numerous foci of a less distinct nature and which appear like enlarged and lighter coloured liver lobules, measuring 2 to 3 mm. in diameter.

Microscopically (Figs. 73, 74, 75, and 76) the liver shows all gradations from more or less normal lobules through enlarged lobules to definitely circumscribed rounded growths. These larger foci may be very thinly encapsulated and in parts not clearly separated from adjacent hyperplastic liver lobules (Fig. 74), or they may be thickly encapsulated and clearly demarcated from the surrounding tissue (Fig. 73). These foci have a purely capillary stroma and lobulation is absent, although sometimes the trabeculae of cells of which they are composed may show traces of a radiating arrangement around a wider vessel reminiscent of a central vein. For the rest the cell-cords are irregularly arranged. They are usually two cells in thickness and are bordered on each side by a capillary whose endothelium is in direct contact with the tumour cells; but often there are wider strands or more solid areas of cells in which more than half-a-dozen elements may be in direct apposition without intervening capillaries. The cells are clearly of the type of liver cells and show considerable anaplastic changes. They are polyhedral, but vary so much in size and finer morphology that it is difficult to apply a general description to them. In diameter they vary from *ca.* 7μ *to* 35μ, the majority being some 15μ but there are areas where smaller and areas where larger cells predominate. The cytoplasm is in general more coarsely granular than that of the normal liver cell, the granules being often somewhat widely separated; but on the other hand many cells have a denser and more homogenous cytoplasm not differing from that of the normal liver cell. The staining reaction varies from definitely basophilic to definitely acidophilic. Areas of greater anaplasia incline to be more deeply basophilic. In general (Fig. 75) the nuclei are moderately uniform in size and shape, are rounded to slightly oval, and measure 4·5μ to 7·5μ in diameter; their nucleoli are single and central and the n : N ratio reaches a maximum of 1 : 9. But in areas of greater anaplasia (Fig. 76) there are marked variations in the nuclei, especially enlargement, and in such places the average nuclear diameter may be 8μ; these nuclei tend to be more markedly oval and are often somewhat angular or irregular in outline. They frequently reach 12μ in diameter. Here the single or frequently double (sometimes triple) nucleoli are still more prominent, n : N ratios of 1 : 9 are frequent and actually reach 1 : 5, the nuclei are often markedly hyperchromatic, and mitotic figures frequent (e.g. one per " oil-immersion field "). The cytoplasm is dense and deeply basophilic. Rare cells may be seen measuring 20μ in diameter (Fig. 76); they may show abnormalities of mitosis (" aberrant " chromosomes and enlarged chromosomes).

These large nodules cause considerable compression of the neighbouring liver tissue.

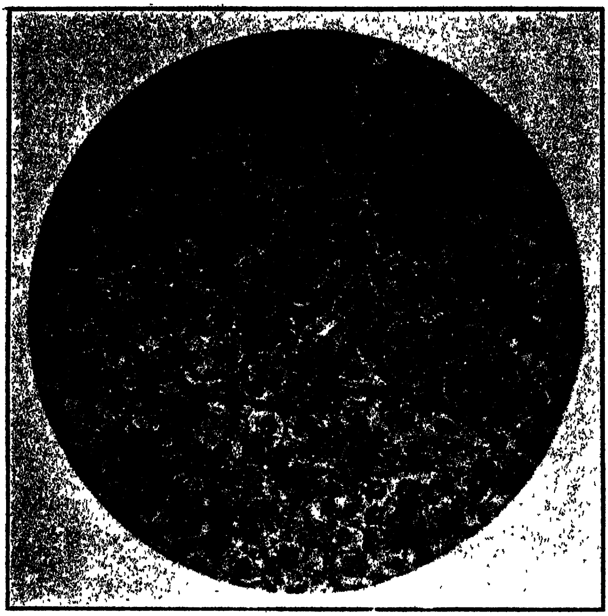

FIG. 75.—Structure of the liver cell adenoma of the pig shown in fig. 73 : Little anaplasia, regularity of cells ; note mitotic figure in centre of field. (6454 ; 250 ×.)

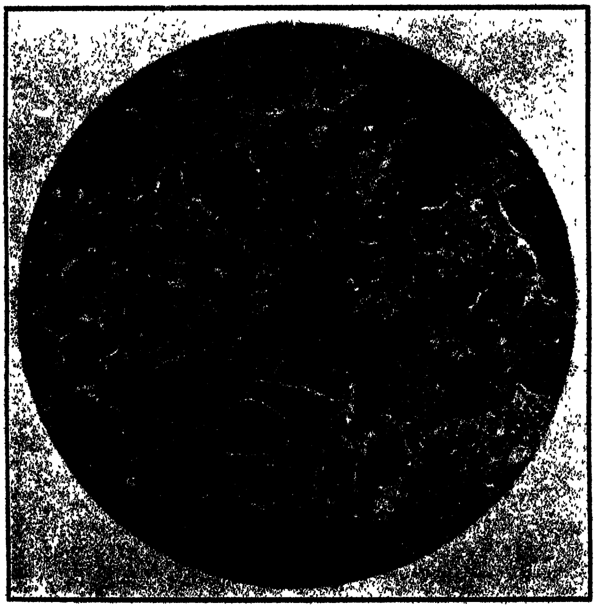

FIG. 76.—Structure of the nodular hyperplasia of the pig's liver shown in fig. 74 : A field showing considerable anaplasia ; note the variation in cell size and the large cell in mitosis. (6454 ; 250 ×.)

The remaining liver tissue shows varying degrees of abnormality of the lobules. They are more unequal in size than in the normal pig liver, some actually approaching in size the larger circumscribed nodules described above. The cells in some lobules average 20 to 23μ in diameter (an extreme size for the normal liver cell). In parts the nuclei average *ca.* 10μ in diameter (a quite exceptional size for the normal liver cell which varies from 6μ to 9μ usually). Often the cells are more basophilic than normal. Occasional large (giant) cells with dense cytoplasm and a bizarre lobed or twisted nucleus occur. The nucleoli may be more prominent than normal and often the nuclei are hyperchromatic. The n : N ratio in a number of the cells reaches 1 : 14, other (contiguous) cells may show a normal ratio (viz. 1 : 25 to 1 : 33). There may be pronounced variation of the staining reaction of the cells in one and the same lobule. There are also within the lobules foci where the cells show a marked fatty infiltration. The pattern of the trabeculae of cells may show disturbance in respect of the normal radial arrangement around the central vein. There is often a considerable engorgement of the intralobular sinusoids with blood. A moderate lymphocytic infiltration occurs fairly regularly in Glisson's capsule and a few eosinophiles are also present here. There is no distinct increase of connective tissue. Granular bile-pigment may be seen within the liver cells and haemosiderin within the Kupffer cells. Neither of these pigments is seen in the larger nodular growths.

Remarks.—The lesions are of a primary multiple nature and vary from more or less abnormal hyperplastic lobules to nodules which must be regarded as having reached neoplastic grade. The process is characterised by varying degrees of cellular anaplasia, and disturbance or complete replacement of the structure of the liver. While the larger nodules are regarded as actual multiple tumours, it must be remembered that there are all gradations between these and lesions which are still no more than hyperplasias. In respect of the anaplasia too there occur varying degrees, some of the nodules having a more "adenomatoid" and others almost a frankly "carcinomatoid" appearance. Nowhere however can actual invasive growth be detected and while it may seem probable that some of the lesions are forerunners of malignancy, the latter description could not be applied to the process in its present stage.

Diagnosis.—Multiple primary hepatocellular adenomata and adenomatoid hyperplasia of the liver.

Case 12 (*Porcine*, 6460).

Macroscopically—in this case also there are only fragments of a pig's liver. On section the appearance seen is much as in the previous case. The lobules are most unequal in size, the larger ones being *ca.* 3 mm. in diameter—(normal lobules up to 1·8 mm.). In addition there are still larger, rounded, sharply defined, and circumscribed nodules up to 7 mm. in diameter. Between these and the enlarged lobules there appear to be intergrades.

Microscopically (Figs. 77 and 78), the picture is much the same as in the previous case except that the nodules do not reach such large dimensions and they are always thickly encapsulated. Within the nodules the normal liver architecture is disturbed. A central vein is absent and the cell cords, as seen in transverse section, regularly enclose minute and indistinct (*ca.* 1μ) lumina around which the cells are radially disposed. The nuclei are inclined to be enlarged and sometimes show angularity of outline. The nucleoli are moderately enlarged (n : N ratio reaches 1 : 16). The cytoplasm is still acidophilic but less so than that of the normal liver cells. Occasional mitoses are seen. Small accumulations of round cells occur. In the liver lobules (Fig. 79) cell abnormalities are also to be seen: hyperchromasia, rare enlarged cells with irregularly lobed nuclei, and disturbance of the radial arrangement of the cell cords. These changes are very unevenly distributed so that, as in the previous case, a patchy appearance results. There are areas where the intralobular capillaries are much congested with blood and there are localised intralobular foci of fatty changes. Stasis of lymphocytes in some of the capillaries is seen. Glisson's capsule shows infiltration with lymphocytes and monocytes, but little detectable increase of connective tissue.

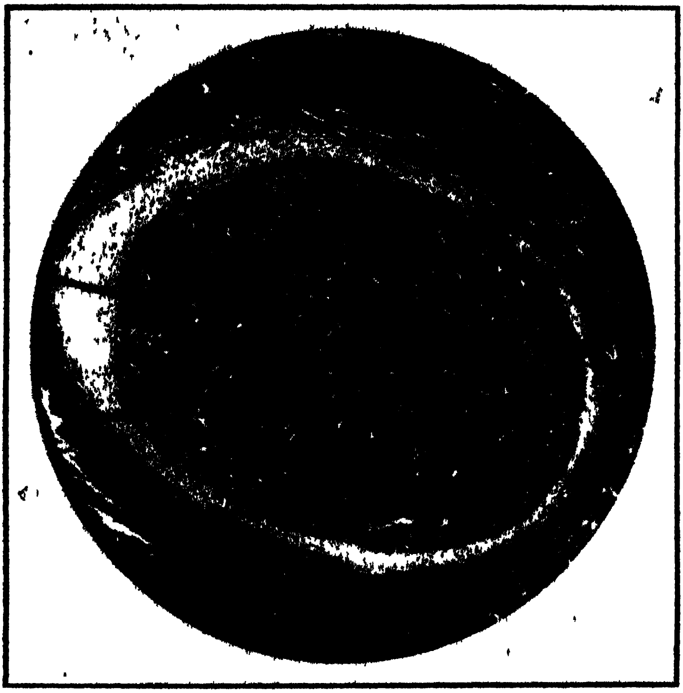

FIG. 77.—Another case of hepatocellular adenoma in the pig; sharp encapsulation against the hepatic tissue. (6460; 33×).

Remarks.—The lesions are essentially identical with those seen in Case 11 (Porcine, 6554), but the extreme anaplastic changes seen in that case are here much less marked. It is probably open to debate whether the encapsulated nodules in this case have actually reached " neoplastic grade ", but I think that such an argument would be a sterile one.

Diagnosis.—Multiple primary hepatocellular adenomata and adenomatoid hyperplasia of the liver.

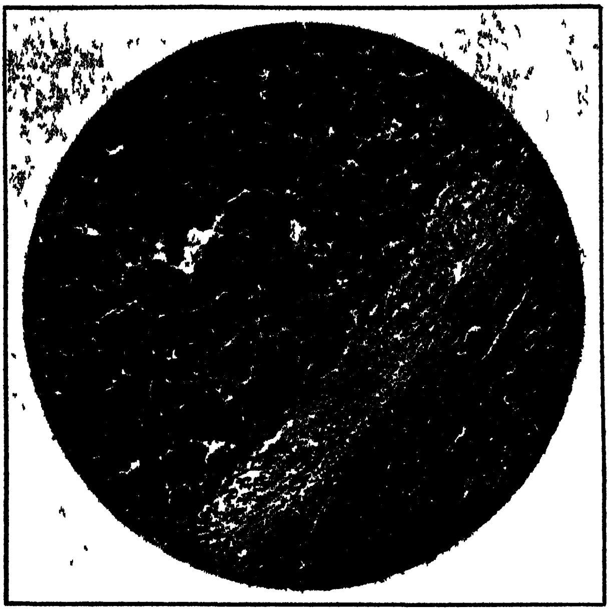

FIG. 78.—Detailed structure of the tumour shown in fig. 77: Atypical arrangement of the cells as compared with those of the liver tissue, right. (6460, 110×).

Case 13 (*Canine*, 15049).

The subject was a male fox terrier, 8 years of age, destroyed on account of acanthoma of the inguinal region. The liver, apart from changes (hyperaemia, etc.), associated with the injection of a lethal dose of chloroform, shows multiple (six) scattered foci as follows:—(1) The caudate lobe towards its ventral border shows a circumscribed, non-encapsulated focus 1·3 cm. in diameter, scarcely visible on the caudal surface but definitely raised above the cranial surface. On section it extends deeply into the liver substance, almost but not quite reaching the caudal surface. In consistence it resembles the liver tissue, but it is slightly lighter in colour and not distinctly lobular in structure. (2) A similar focus occupies the right part of the right central lobe near the fundus of the gall-bladder, being raised above the caudal surface of the liver and measuring 2 mm. in diameter. (3) The upper part of the lateral border of the left lateral lobe shows an oval focus, 1 cm. × 75 cm., raised about 2 mm. above the caudal surface; this is not distinguished clearly from the liver tissue by colour, but only by absence of lobulation. (4) and (5) On the cranial surface of the left lateral lobe towards the left border are present two barely visible foci, *ca.* 1·5 mm. in diameter, very slightly raised above the surface. (6) The right central lobe shows a focus of similar appearance to numbers (4) and (5) and measuring 2 mm. in diameter. There are also a few scattered (pin-head sized to ·5 mm.) bluish-red subcapsular foci, extending 1 mm. into the substance of the liver.

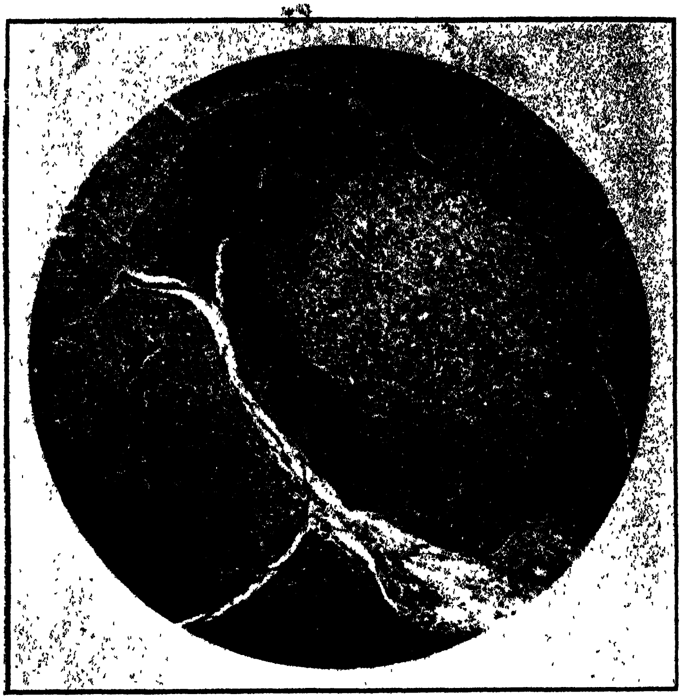

FIG. 79.—Intralobular hyperplasia in the liver of the same subject as figs. 77 and 78: Note irregularity in size of the liver lobules, one of which contains a non-circumscribed focus composed of atypically arranged and anaplastic liver cells. (6460; 40×).

Microscopically, in the liver are seen sharply circumscribed but unencapsulated foci which consist of atypical hepatic parenchyma. Their distinction from the surrounding normal tissue is far less striking under the microscope than to the naked eye. The lobulation in these areas is deficient, but by no means always absent. In parts the lobulation may fail or be masked by the large size attained by the lobules. The columns of liver cells are less regular in arrangement. Bile-ducts are present, no differences in pigment content are noticed, nor are differences in size and shape and the nuclei of the cells seen. The cells composing these foci appear more closely packed than in the normal liver tissue, the whole having a denser appearance than the normal parenchyma. There is no increase of connective tissue. The subcapsular foci noticed macroscopically are small haemorrhages where macrophages carrying haemosiderin, and also giant cells are active. For the rest, the liver, apart from slight fatty changes and a hyperaemia associated with the chloroform poisoning, is normal.

Diagnosis.—Multiple nodular hyperplasia of the liver.

In conclusion, attention may be drawn to the peculiar hypertrophic liver lesion in the sheep (12196) shown in Fig. 80. The condition may possibly be mistaken for a hyperplastic or even benign neoplastic process.

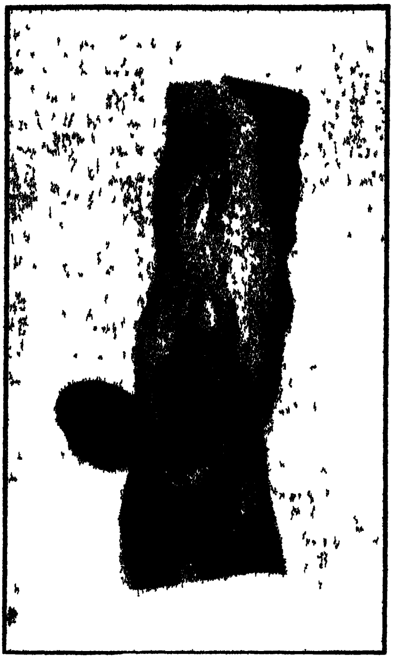

FIG. 80.—A peculiar local hypertrophy of the liver of a sheep: A nodule of structurally normal liver tissue invaginates the wall and protrudes prominently into the lumen of the vena cava as it passes through the liver (12196, 1.2×).

Summary of the Pathology of Cases of non-malignant proliferative processes.

The bovine case is to be regarded as a typical solitary adenoma and it is interesting to compare this with the cases diagnosed as carcinoma. We see that the essential difference here is the absence of invasive growth which might lead to metastasis. This is not dependent on encapsulation, for we have described cases of malignancy which were well encapsulated, and in this benign tumour encapsulation is most incomplete. The histopathology much resembles that of the carcinomas. Certain differences are present but they are nearly all differences of degree; and, bearing in mind the experience in man in which it has been found impossible to discriminate sharply between benign and malignant "hepatomas" on the basis of morphology, one would here be very hesitant of generalising on the basis of a single case. The differences referred to may be summarised as follows:- The cytoplasm of the cells resembles that of the liver cells in staining reaction, while in the carcinomas there is an (inconstant) tendency to basophilia. The nuclei, although (as is also the case in carcinomas) distinctly enlarged, are more uniform in size than in most of the carcinomas. The nucleoli show no distinct enlargement in proportion to the nuclei, while such enlargement although by no means affecting every cell could usually be found in the carcinomas. Mitotic figures were absent, whereas a low mitotic index was always found in the malignant tumours in bovines, although not always in the sheep. It must be emphasised that this tumour could not be distinguished macroscopically from many of those diagnosed as carcinomas, a detailed microscopic analysis, especially the demonstration by examination of an adequate number of representative sections of the absence of invasive growth, providing the only means of differential diagnosis. That the purely morphological criteria mentioned are not likely to be constant in occurrence will be apparent from the two cases in pigs which may now be briefly discussed.

In these two cases in pigs the lesions are of a primary multiple nature and are very different in appearance. There are all grades of transition from lesions which we have called adenomatoid or nodular hyperplasia to tumours. These tumours and hyperplasias, in spite of their benign nature, show marked anaplastic changes affecting the cells to an extent fully equal to that found in the carcinomas. Regarding increase in nucleolar size actually larger ratios (1 : 5) were found than among any of the carcinoma cells except if we take into account the markedly altered nucleoli of the nature of inclusion bodies. In the malignant cases, ratios of more than 1 : 9 were only exceptionally encountered. Further, in these porcine tumours cytoplasmic basophilia, irregularity of cell size, giant cells, frequency of mitotic figures, some of which actually appeared abnormal, and enlargement and irregularity of the nuclei were present to an extent fully commensurate with what was found in the malignant tumours of ruminants.

This serves to emphasize again the unreliability of morphological criteria in the estimation of liver-cell tumours and that cell changes especially should not receive too much stress, because marked degrees of anaplasia may occur not only in benign tumours but also in areas of hyperplasia which have not yet reached neoplastic grade. It is perhaps not quite fair to say that such observations disprove the contention of MacCarty and Hammeder that relative nucleolar enlargement is a constant and specific accompaniment of malignancy. The reply might well be that no hard and fast lines can be drawn between these various proliferations of liver cells and that the lesions which we call an adenoma, or a hyperplasia, may well be direct forerunners of malignancy if not actually early stages of cancer. However, so far as the liver tumours are concerned, the contention cannot be accepted without being modified as we have indicated. While a study of the morphology of these pathological processes fully supports the idea that adenomas may be derived from hyperplasias and carcinomas from adenomas, yet it seems most unlikely that every nodular hyperplasia is destined to reach a neoplastic grade and that every adenoma is an early carcinoma. The lesion may progress no further. Indeed, we know in some species, and this brings us to the consideration of the case described in the dog, that nodular hyperplasia does not lead to neoplasia. Nodular hyperplasia is well known in this species, yet liver-cell carcinoma is unknown. The lesions which we have described in the dog have been included here mainly for the sake of completeness; they are not neoplastic and are in no danger of becoming so. The degree of imitation of normal liver tissue is very close and anaplastic changes are conspicuous by their absence.

II. Cholangiocellular Tumours.

A. MALIGNANT CHOLANGIOCELLULAR TUMOURS.

It is a remarkable but a well-known fact that the incidence of the tumours of bile-duct epithelium and those of liver cells shows a distinct species specificity. Thus in man cholangiocellular carcinoma is rare while hepatocellular carcinoma is by comparison common. In the domestic carnivores cholangiocellular carcinoma is common, hepatocellular unknown. In the ruminants, hepatocellular carcinoma is extremely common while the cholangiocellular tumours are considered rare. The Onderstepoort collection contains four examples of cholangiocellular carcinoma in the bovine and one in the dog.

From the human literature we gather that there is considerable confusion regarding the distinction of the two varieties of primary liver carcinoma. Among domestic animals we have not encountered this difficulty and the only confusion likely to arise in our experience is the separation of primary bile-duct tumours from secondary carcinoma.

Case 14 (*Bovine*, 5771).

The museum specimen consists of a slice of a large tumour taken from a bovine liver. The size of the whole neoplasm cannot be given, but it must have measured considerably more than 18 cm. in diameter. It has a greyish-yellow colour (preserved) and shows a fairly prominent connective-tissue stroma subdividing the parenchyma into irregularly rounded areas ·5 to 1 cm. in diameter, having opaque, yellowish-white contents.

Microscopically, sections which transect the margin between the tumour and the liver disclose an extremely defective encapsulation, there being direct invasion of the hepatic parenchyma at many points. There is a branching connective-tissue stroma marking out the gross lobules observed macroscopically, and finer trabeculae separating secondary lobules some 50 to 175μ in diameter. These may have the structure of a single acinus or tubule lined by columnar epithelial cells enclosing a distinct lumen which is usually plugged by desquamated and necrosed tumour cells; or there may be multiple smaller acini in the lobule, lined by radiating columnar cells and showing smaller lumina (*ca.* 15μ), or the lumina may be almost or entirely obliterated because the free cytoplasmic poles of the cells meet centrally. These acini are not backed by connective tissue and pass somewhat indefinitely one into another. In many of the secondary lobules, however, the structure is solid and there is no evident cell polarity. Between these and the lumen-containing lobules there are all grades of transition and the larger tubules have walls which are often, in whole or in part, several cells thick. The cells lining tubules are of an outspoken columnar form and have a non-granular acidophilic cytoplasm with a short-oval to definitely elongate-oval nucleus which has a distinctly proximal location (i.e. remote from the lumen), leaving a free distal area of cytoplasm bordering the lumen. This distal portion of the cytoplasm is strongly eosinophilic and appears, with that of the other cells, to form a continuous condensed cytoplasmic lining to the tubule. The nuclei do not stain intensely (except in necrobiotic cells, where they are pycnotic) and have a finely granular chromatin. They have one to two nucleoli which are centrally or eccentrically located. These are scarcely conspicuous, the n : N ratio seldom exceeding 1 : 25 while the average is 1 : 32. (On the other hand, they must be considered as enlarged since in the normal bovine bile-duct epithelium the ratio is seldom greater than 1 : 50.) The cells thus have a close resemblance to bile-duct epithelium: their cytoplasm stains identically, the position of the nucleus is similar, and the chromatin pattern identical.

Outside the main mass, smaller masses of the same tumour tissue are found in the liver spreading along the portal tracts and from here invading the parenchyma, and extensive tumour cell embolism is to be seen in veins at the margin of the tumour. Mitoses are fairly frequent (Index – 3). The surrounding liver tissue shows a marked cirrhosis which is mainly perilobular in type.

Remarks.—A massive tumour showing invasive growth and formation of local blood-borne metastases and composed of cells having an unmistakable resemblance to bile-duct epithelium and forming outspoken lumina in its less anaplastic portions.

Diagnosis.—Carcinoma cholangiocellulare.

Case 15 (*Bovine*, 10764).

The museum specimen (Fig. 81) consists of a slice of a large neoplastic mass some 12 cm. in diameter infiltrating and replacing the liver tissue. It is of a creamy yellow colour and of soft, gland-like consistence. It is unencapsulated. Occasional strands of connective tissue course through it and at the periphery appear to become continuous with that of the portal tracts. In places a thin (1 to 7 mm.) rind of liver tissue persists between the neoplasm and the capsule of the liver; elsewhere the tumour is covered directly by the liver capsule, which is intact. Small cystic cavities (up to ·5 mm. in diameter) pervade the tissue and contain opaque, yellowish-white material.

Microscopically, a moderately well differentiated and rather regular connective-tissue stroma supports lobules of epithelial cells. These lobules are typically subdivided into multiple acini lined by a single row of columnar cells whose nuclei are situated distinctly proximally, are spherical or slightly oval, and have a delicate chromatin network (i.e. for epithelial nuclei, they are amblychromatic). The nuclei usually measure 6 to 7·5μ in diameter and are rather uniform in size. They may seldom tend to be of elongate oval shape (only in limited parts). The nucleoli are large, single, and often depart from the spherical shape to assume an oval, angular, or rectangular form; not seldom they are ring-like, having a central vacuole or area of rarefaction. The n : N ratio is seldom less than

1 : 25 and reaches 1 : 9. Centrally no lumen is usually visible, the free cytoplasmic poles of the cells meeting each other. On the other hand the cells may be arranged in solid alveoli, in which case only those next to the stroma may retain the polarised appearance, the central cells being rounded or polyhedral with central nuclei. Centrally in many of the lobules there is necrosis, the cells having degenerated to form a caseous mass in which calcification may be taking place. There also occur among the cells many hyaline, eosinophilic globules, often showing concentric lamellation. Mitotic index = 2.

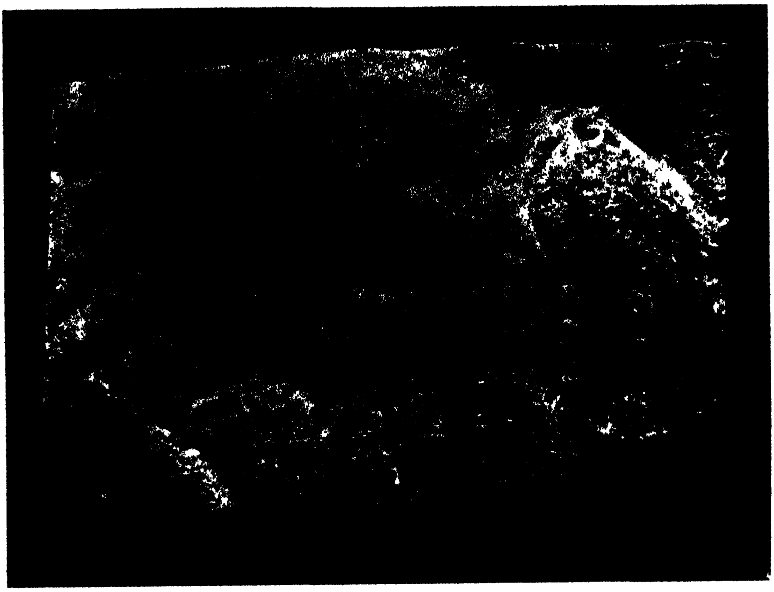

FIG. 81.—Naked-eye appearance of a typical cholangiocellular carcinoma of the ox: Multiple closely set, minute cystic cavities permeate the tissue; contrast with the hepatocellular tumours, figs. 61 and 72. (10764; natural size).

Remarks.—This tumour resembles the more anaplastic portions of the previous case, and would scarcely be recognised as a cholangiocellular tumour by one who had not studied such a case and observed the transition (which was there remarked on) from a bile-duct type of morphology to rosettes without lumina and to completely solid alveoli of non-polarised cells. It is only on the basis of that experience, and on the general resemblance of the cells to the less differentiated elements formed in that bile-duct carcinoma that we were able to arrive at a diagnosis.

A tumour of the rumen was reported by the sender of the material to have been present in this subject. This was not submitted, but a lymph-gland was sent in. It might be thought that one would be cautious in diagnosing a primary liver cell tumour in the presence of a primary tumour elsewhere; but glandular tumours do not occur in the rumen, all epithelial neoplasms being of the

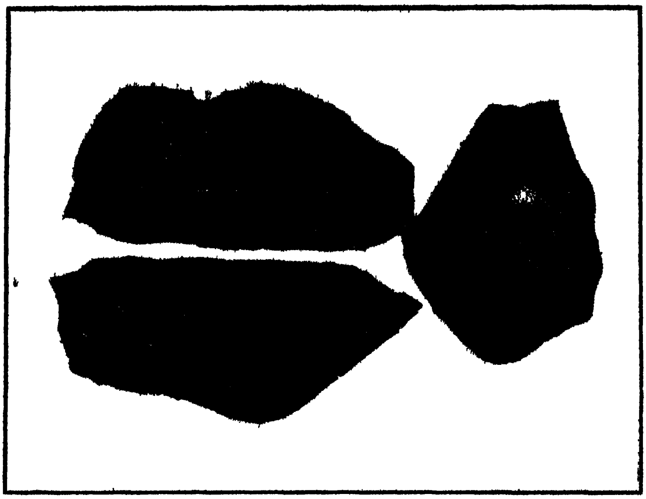

FIG. 82.—Cholangiocellular carcinoma of the bovine. Invasive spread in the liver; contrast with the hepatocellular tumours figs. 61 and 72. (10765, 2/5×)

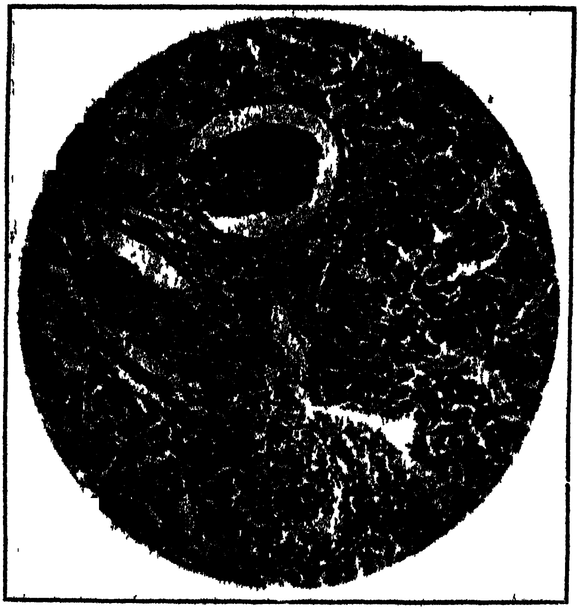

FIG. 83.—Structure of the cholangiocellular carcinoma of the bovine shown in fig. 82. Invasion of a vein of the stroma. (10765; 240×)

squamous type. In the present case the lymph-node, on section, proves to contain typical metastases of acanthoma. These lesions can therefore have no relation to the tumour described.

Diagnosis.—Carcinoma cholangiocellulare.

Case 16 (*Bovine*, 10765).

The museum specimen (Fig. 82) consists of portions of an irregularly oval neoplasm infiltrating and replacing the liver tissue and measuring some 10 × 4 cm. It is not encapsulated from the liver tissue. The colour is yellowish-white. There occur comparatively rare, minute, cyst-like cavities with opaque caseous contents and measuring *ca.* ·5 cm. In parts the margin is exceedingly irregular and an intimate penetration of the surrounding tissue is seen. In parts also portions of the liver tissue remain within the tumour and give a greenish colouration to the otherwise yellowish-white mass. A distinct system of coarse connective-tissue trabeculae is present demarcating large areas one or more cm. in diameter and finer trabeculae can also be seen to demarcate lobules usually 1 to 2 mm. in diameter. The regional lymph-nodes were stated to have been affected and sections thereof are available.

Microscopically (Fig. 83) there is a resemblance of the primary tumour to the previous case (15) but far less differentiation occurs. There is a rich collagenous stroma demarcating the smaller lobules noticed macroscopically and within these still finer collagenous strands demarcate solid alveoli of cells. Only rarely are the faintest traces of lumen formation seen and rosette formations are absent. The cells show no polarity and are gathered into irregular solid masses. They bear no resemblance to liver cells, but in spite of their lack of differentiation are very similar to those described in the previous case. Their cytoplasm stains palely and tends to be faintly eosinophilic. The nuclei are short-oval, fairly often tending to be elongate-oval, variable in diameter from *ca.* 6μ to over 10μ. They stain palely in the more typical cells, but in most cells there is considerable hyperchromasia and the nuclei may be filled with fine granules. There is however no resemblance to the pattern of the liver-cell nucleus and (discounting the secondary changes) a definite similarity to the bile-duct cell nucleus. The nucleoli are usually single, but 2, 3 or 4 may be seen; the n : N ratio is commonly 1 : 26 and reaches 1 : 14. Commonly, especially towards the edge of the tumour, strands of atrophic liver cells persist among the lobules. There is little necrosis. At the edges active infiltration is taking place along Glisson's capsule, and at the extreme edge of this advance the masses of tumour cells are seen to occupy pre-formed endothelial-lined spaces (lymphatics) in the portal tracts. Further towards the centre of the tumour the (older) portal tract infiltrations are no longer confined but spread into the contiguous hepatic parenchyma and there is a lymphocytic infiltration of Glisson's capsule. The surrounding hepatic tissue shows a pronounced blood stasis in the intralobular capillaries and also multiple small haemorrhages. The mitotic index = 3.

The regional lymph-node shows a similar tumour growth (Fig. 84) which has all but obliterated the lymphatic tissue. Unexpectedly, although a large amount of the neoplastic tissue has the same undifferentiated appearance as the primary, there are many areas with distinct rosettes and also outspoken lumina lined by columnar cells with proximally situated elongated nuclei, clearly resembling bile-ducts, as described in case 15. There are also seen, although to a less marked degree, the condensation and eosinophilia of the free (peripheral) cytoplasmic pole which was there described.

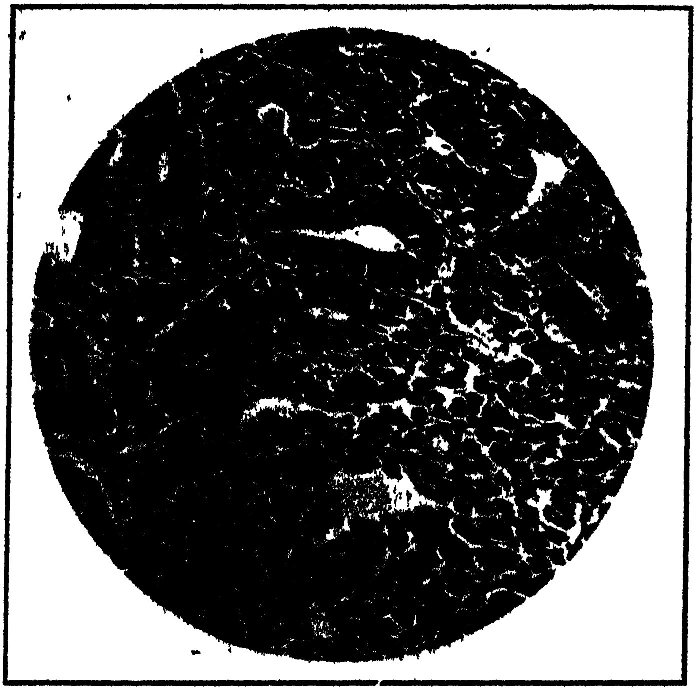

FIG. 84.—Regional lymph-node metastases of the cholangiocellular carcinoma, shown in figs. 82 and 83: Decrease in anaplasia with lumen-formation; below, transition to the highly anaplastic growth-mode of the primary. (10765; 240×).

Remarks.—The diagnosis of this highly anaplastic tumour is greatly facilitated by the fortunate and unusual circumstance that the lymph-node metastases show a greater degree of differentiation allowing a clear recognition of the bile-duct type of tumour.

Diagnosis.—Carcinoma cholangiocellulare with metastasis to the periportal lymph-node.

Case 17 (*Bovine*, 6278).

The subject, a bovine whose age and sex were not recorded, had been slaughtered at the Pretoria Abattoirs, and from a macroscopic description made at the time(⁷) one gains the following information:

(⁷) By Dr. P. J. Fourie, to whom I am indebted for permission to describe the case.

Widely distributed multiple nodular growths affected both parietal and visceral abdominal serosae. The parietal peritoneum was extensively affected by numerous tumours which were irregularly scattered, although especially numerous on the lateral walls of the peritoneal cavity; these tumours extended also into the pelvis, affected the sublumbar and iliac regions, the serosa covering both the muscular and the tendinous portions of the diaphragm, and, in limited numbers, also the abdominal floor. They often occurred in clusters and reached a size of 9 cm. × 4 cm., being sometimes as much as 2·5 cm. in height above the surrounding surface. When confluent, they resembled the "grapes" of serosal tuberculosis. The smaller tumours may measure ·5 cm. in diameter. They are confined to the serosa and do not invade the underlying musculature. The left lateral ligament of the liver (as well as the diaphragm) was affected by numerous tumours varying in size from 2 mm. to 5 cm. in diameter. The smaller tumours are described as spherical, the larger ones as irregular in outline, vertically compressed, and showing a lobulated surface. Some of those affecting the diaphragm were continuous through the thickness of the latter with tumours appearing on the pleural surface thereof. The neoplasm had a uniform greyish-white colour. Tumours were further numerous on the visceral surface of the liver, appearing as confluent, conglomerate masses. The largest tumour measured 20 × 10 × 5 cm. and was situated for the most part within the substance of the liver. It is irregularly ovoid in shape and is composed of a number of large ovoid lobes, 5 to 6 cm. in diameter, some of which are more sharply demarcated than others. Near its circumference are outlying nodules in the liver tissue of similar appearance, and measuring *ca.* 3 cm. in diameter. This largest mass was described as a very firm consistence (almost "cartilaginous") and has a light yellow colour. At parts of its circumference it is thinly encapsulated, at other parts it gradually merges with the surrounding hepatic tissue. On section, with the naked eye is seen a prominent connective-tissue stroma whose disposition is very irregular and which contains a few blood-vessels (in transection of pinhead size). No lumina or cystic cavities are visible in the parenchyma. Many smaller tumours affected only the surface of the organ. The lesser omentum was affected by small tumours. The parietal surface of the liver (right lobe) showed about a dozen discrete small nodules varying in diameter from 1 mm. to 1·5 cm., completely circumscribed and confined to the capsule. Some half-dozen small tumours 5 mm. to 2 cm. in diameter affected the serosa of the gall-bladder. The caudal mediastinal lymph-node was enlarged, both medulla and cortex showing circumscribed nodules, ·5 to 1 cm. in diameter, of similar appearance to the peritoneal nodules and sometimes bulging above the surface of the gland. The periportal lymph-nodes were also affected. The other organs showed no changes relevant to our purpose (echinococcosis of the lungs and fibrosis of the pancreas).

The material actually available to me for examination (Figs. 85 and 86) consists of portions of the parietal peritoneum and diaphragm bearing multiple, broadly attached and somewhat flattened nodules, elevated to a height of 2 cm. above the surrounding surface, and varying in diameter from 1 to 5 cm. They have a lobulated surface. They do not penetrate the subserous fat. Their

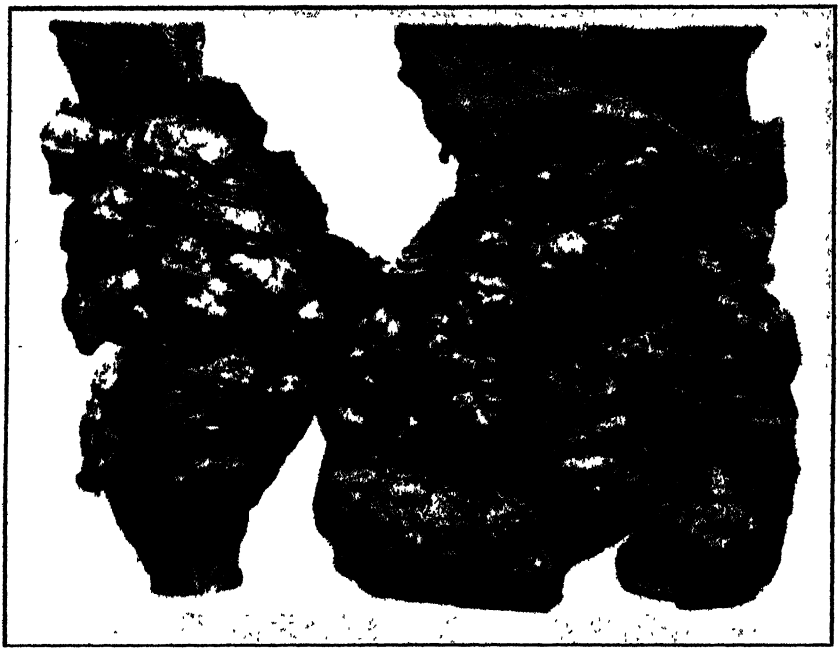

FIG. 85.

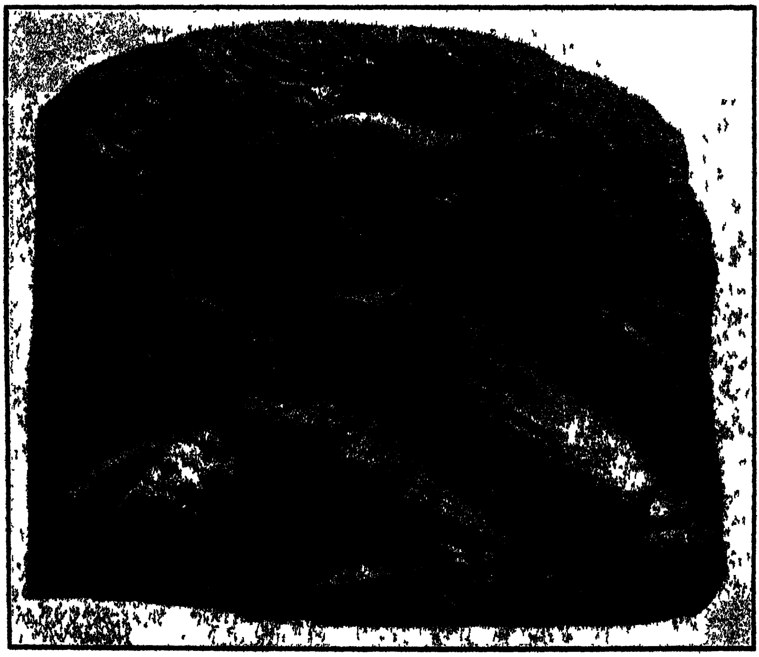

FIG. 86.

FIGS. 85 and 86.—Gross appearance of secondary serosal carcinosis of the ox: Secondary lesions of *c. cholangiocellulare* affecting the subserosa of the diaphragm (fig. 85) and costal peritoneum (fig. 86). (6278; 1/3×).

surface is uneven, but glistening, thus apparently definitely subserous in position. In addition to these, there are available a slice of the large liver tumour and microscopic sections of the lymph-nodes which had previously been cut.

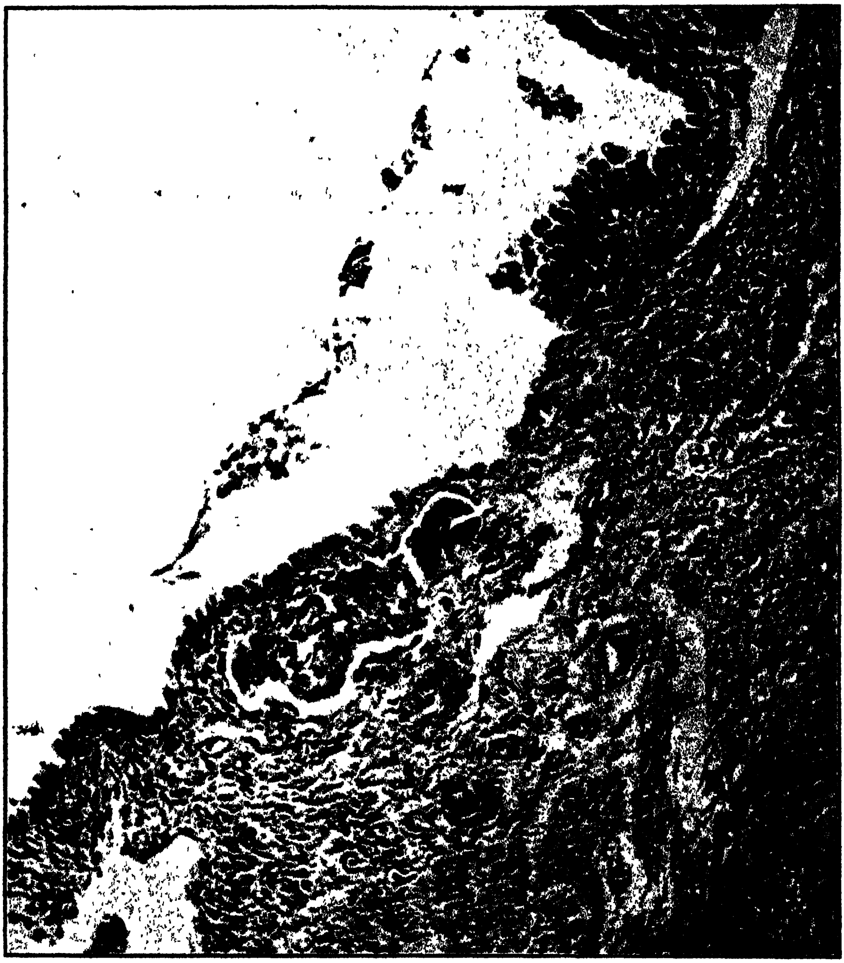

FIG. 87.—Serosal carcinosis of the ox (from the lesions shown in figs. 85 and 86) secondary to carcinoma cholangiocellulare of the liver: Mobilisation of the lining cells of the peritoneum to form papilliform elevations (especially above); this is interpreted as a collateral hyperplasia and there is no continuity with the tumour cells which lie within the lymphatics immediately below. (6278; 240 ×).

Microscopically (Fig. 87), sections of the parietal peritoneal tumours show that these consist of a very rich and often highly cellular connective-tissue stroma demarcating islands and strands of polygonal cells, which have a marked resemblance to those seen in the previous case (Bovine, 10765). The cells are, however, on account of the cold storage preceding fixation, less well preserved, especially in respect of their cytoplasm. The stroma is often so prominent as to produce a scirrhous appearance, and especially in the more superficial parts of the subserosa (Fig. 87), it seems that the widely separated parenchymal units lie largely in pre-formed spaces to which sometimes traces of an endothelial lining can still be recognised. However, in the deeper parts, the parenchyma is present in larger amount and in more massive tracts and appears to be spreading extravascularly along the cleavage lines of the (much increased) connective tissue.

The cells are polygonal elements aggregated into narrow strands or rounded alveoli by the connective-tissue stroma. An intercellular reticulum is absent. On account of the poor preservation, the cytoplasm is indistinctly outlined, but the cells often measure some 15μ in diameter. The cytoplasm stains a violet-mauve with haemalum-eosin, except in compressed strands of cells having pycnotic nuclei, in which it is more acidophilic (necrobiosis). The nuclei are central, well-preserved, and typically of elongate-oval but also often of short-oval shape. A few are slightly angular or indented. They vary considerably in size from 7·5μ to 12μ in diameter and are rather characteristic in structure, showing a sharp and (as compared, e.g., with a fibroblastic or endothelial nucleus) a slightly pronounced nuclear membrane. There is a uniform, exceedingly fine, but distinct chromatin network throughout the nucleus, which in consequence stains very lightly. In this pale-staining nucleus the single or (equally frequently) double, slightly to extremely eccentric, well-defined, and heavily staining nucleolus is a striking feature. It is usually rounded, quite often oval or somewhat angular, or sometimes dumb-bell shaped, there being transitions between a single dumb-bell shaped structure and two more or less discrete nucleoli. The n : N ratio commonly lies between 1 : 16 and 1 : 25. The large "hyaline", palely staining intranuclear inclusions, which have been described elsewhere (*vide carcinoma hepatocellulare*, etc.) in detail and as being of nucleolar origin are fairly commonly to be found. If these are included in the consideration of the nucleoli, the n : N ratio must be said to reach 1 : 2. (Fig. 8.)

There is a tendency for the nodules to be encapsulated by connective tissue beneath the mesothelium of the surface, but often such encapsulation is most incomplete, the encapsulating tissue being itself prominently infiltrated by the neoplastic cells. Areas of total neocrosis occur in the larger tumours. Sections through some of the nodules show them to be covered by mesothelial cells which in places present a picture of definite mobilisation (Fig. 87). Papilliform structures arise having a core of connective tissue and the mesothelial cells covering these as well as those between their bases assume a cuboidal to columnar shape, and cannot be said to be very dissimilar in their finer morphology to the tumour cells except that (*a*) polarity is fully retained and (*b*) the nucleoli are not so prominent. Thus these proliferating mesothelials would not be obviously distinguishable in morphology from the solid masses of cells which lie within the lumina of the immediately underlying lymphatics of the subserosa; but nowhere is continuity between them traceable, the peritoneal tumours being always beneath the serosa, although they may approach close to it.

Sections of the liver show tumours of similar morphology, either confined to the subserous tissue of the capsule or (in the case of the large intrahepatic tumour—Fig. 88) actually invading the hepatic substance. In the affected lymph-nodes a rich growth of similar type affects and replaces both the cortical and (more especially the medullary zones). Nodules on the splenic surface (Fig. 89) are limited by the capsule of the organ. Mitotic index = 2.

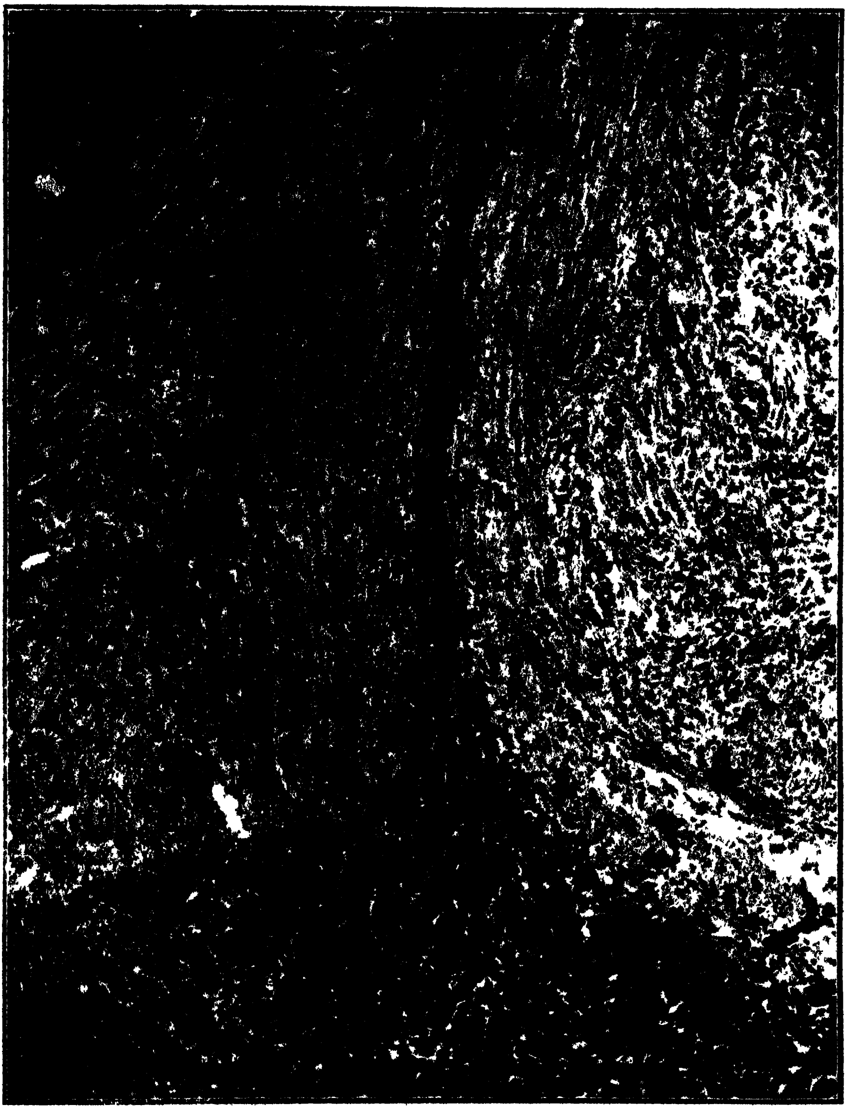

FIG. 88.—Highly anaplastic bovine cholangiocellular carcinoma, invading the liver: Tendency for the cells to be arranged in long parallel rows; centre, a strand of the persisting hepatic parenchyma. (6278; 120 ×).

Remarks.—This case has been described in some detail because it represents a highly anaplastic tumour which is not readily diagnosed and because of the great likelihood of confusing the peritoneal secondaries with primary lesions of the serosae. Its microscopic structure is that of *carcinoma simplex* and there is no trace whatever of the adenoid growth which facilitates recognition of cholangiocellular tumours; one's criteria here have to be, macroscopically, the occurrence of what is apparently the primary lesion in the liver, the well-developed stroma (differentiating from hepatocellular carcinoma); and, microscopically, the amblychromatic staining and typically elongate-oval shape of the nuclei. In actual histological structure, only the tendency to vertical arrangement of the individual cells in the rows which are formed between the stromal strands (Fig. 88) is even remotely suggestive of the structure which we associate with typical bile-duct-cell tumours. The previously-described case (16) provides a fortunate link between such highly anaplastic cholangiocellular tumours (*C. simplex*) and those whose origin is clearly declared by their structure (*C. adenomatosum*). In the present case, the primary tumour, although of considerable dimensions, is overshadowed by the very extensive secondary serosal carcinosis, and the latter lesions might therefore readily be mistaken for primary tumours, more especially on account of the danger of

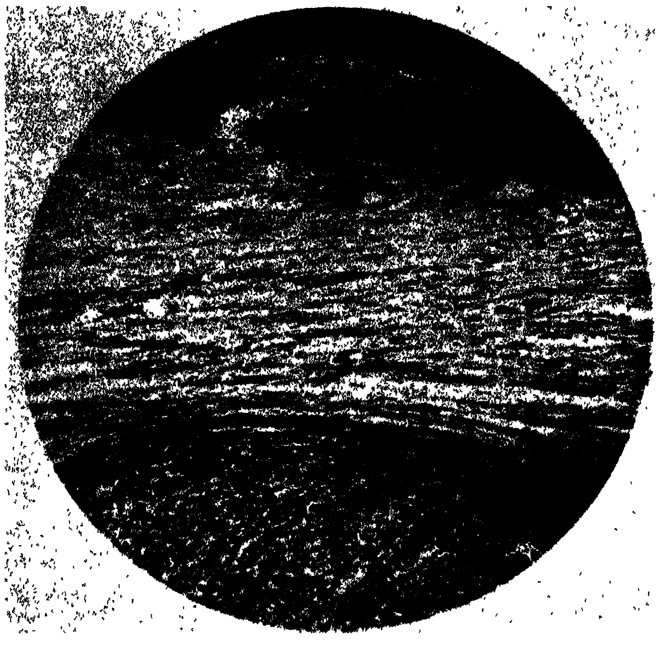

FIG. 89.—Secondary cholangiocellular carcinoma of the ox affecting the subserosa of the spleen; above, the splenic tissue and its capsule. (6278; 65×).

misjudging the collateral hyperplasia of the surface mesothelium as a precancerous change with histogenetic significance. The significance of these remarks will become apparent after the discussion of primary tumours of the serosae in Chapter VI.

Diagnosis.—Carcinoma cholangiocellulare with intrahepatic and regional lymph-node metastases and with widespread secondary peritoneal carcinosis affecting both parietal and visceral serosae.

Case 18 (*Canine*, 15152).

The subject was an Alsatian dog aged 10 years. Macroscopically (Fig. 90) the right lateral lobe of the liver is almost totally replaced by a large, infiltrating, non-encapsulated neoplasm, irregularly oval in shape, measuring 13 x 11 x 6 cm., of gland-like consistence and of a greyish-white colour. It presents an irregular nodular surface beneath the serosa of the liver. There are also multiple scattered nodules usually ·5 mm. to 5 cm. in diameter, some larger by confluence, throughout the remainder of the liver tissue. The periportal lymph-nodes are enlarged and show nodules of a similar appearance situated mainly subcapsularly (i.e. filling the cortical sinus system and sometimes extending inwards into the medulla). The lungs show multiple disseminated metastases varying from 3 to 5 mm. in diameter.

Microscopically (Figs. 91, 92, 93, and 94) the neoplastic tissue in the liver is seen to be unencapsulated and to consist of epithelial cells dispersed in a collagenous stroma and showing considerable variation in arrangement:—(*a*) For the most part [Figs. 91 and 92 (lower part of figure)] the cells form a lining to regular tubules, from one to several cells thick. Here there is a distinct resemblance to bile-ducts and the cells are columnar to cuboidal in shape. Often the lumen is incompletely developed. These neoplastic tubules are actively invading and destroying the liver tissue. There is a proliferation of bile-ducts in the portal tracts and here it is often hard to separate the neoplastic from the hyperplastic tubules on any basis except that of the cell morphology. The neoplastic cells differ from the bile-duct cells chiefly in showing greater variation in cell size, more hyperchromatic nuclei (although they still do not stain deeply, their granules are larger and much more numerous), greater prominence of the nucleoli (seldom less than 1 : 25, often 1 : 9, seldom 1 : 4, as compared with the n : N ratio of the proliferating duct-cells, viz. 1 : 56), and considerable variation in nuclear size (often as much as twice the size of the bile-duct nuclei); a greater tendency for the nuclei to be plump or short-oval, greater density of the cytoplasm which stains more deeply basophilic and is inclined to be very finely granular as compared with the pale staining, homogeneous cytoplasm of the bile-duct cells. The fact that such a comparison has been instituted makes it obvious that a close similarity exists. In the deeper parts of the tumour, however, there are marked differences from bile-ducts which result from thickening of the lining layer of cells, inward growth into the lumen often resulting in total obliteration of the latter, and filling of the lumina by desquamated elements. In those parts where the liver tissue persists, the tumour is seen to be spreading along the portal tracts (Fig. 91), which are

FIG. 90.—Cholangiocellular carcinoma of the dog: Note also (centre) the metastases in the periportal lymph-nodes and (left) multiple small intrahepatic metastases. (15152: 1/3×).

FIG. 91.—Cholangiocellular carcinoma of the dog: Characteristic spread in Glisson's capsule. (15152; 30×).

infiltrated by lymphocytes and neutrophiles and show newly-formed connective tissue. From here the growth also encroaches on the hepatic parenchyma which is congested and in which the cells show varying degrees of degeneration and granular bile-pigmentation, together with marked haemosiderosis of the Kupffer cells. (*b*) In sections from other parts of the tumour there are extensive areas where the cells are arranged to line multiple cysts (Fig. 92—upper part of field), the epithelium varying from tall columnar to cuboidal or even flattened. These cysts contain desquamated cells and are

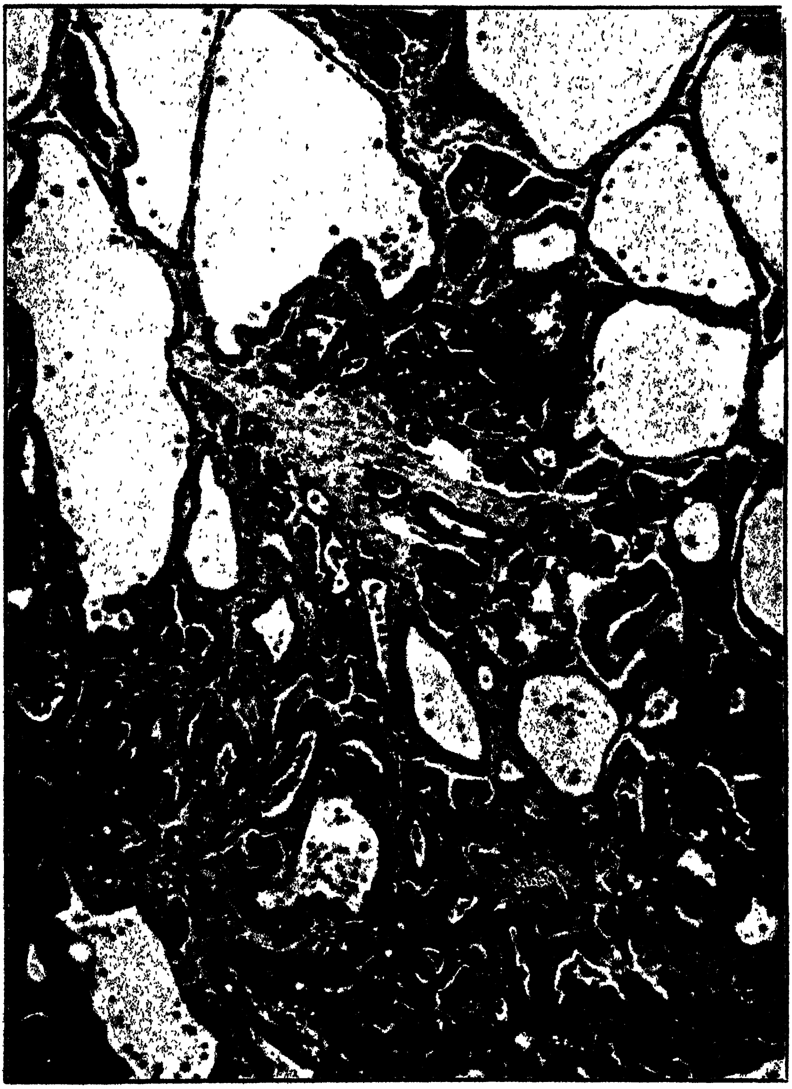

FIG. 92.—Cholangiocellular carcinoma of the dog: Adenoid (below) and cystic (above) types of growth. (15152; 110×).

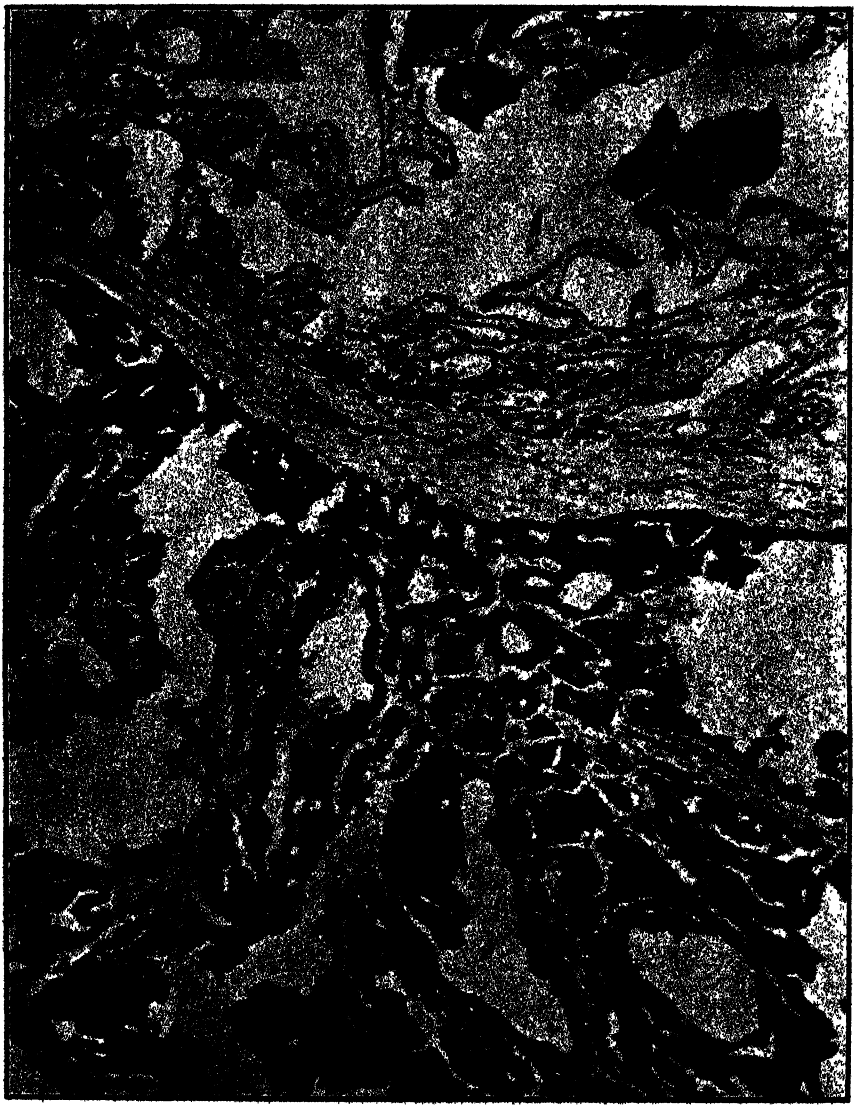

FIG. 93.—Another field of the same tumour shown in figs. 91 and 92: Cystic papilliform type of growth. (15152; 110×).

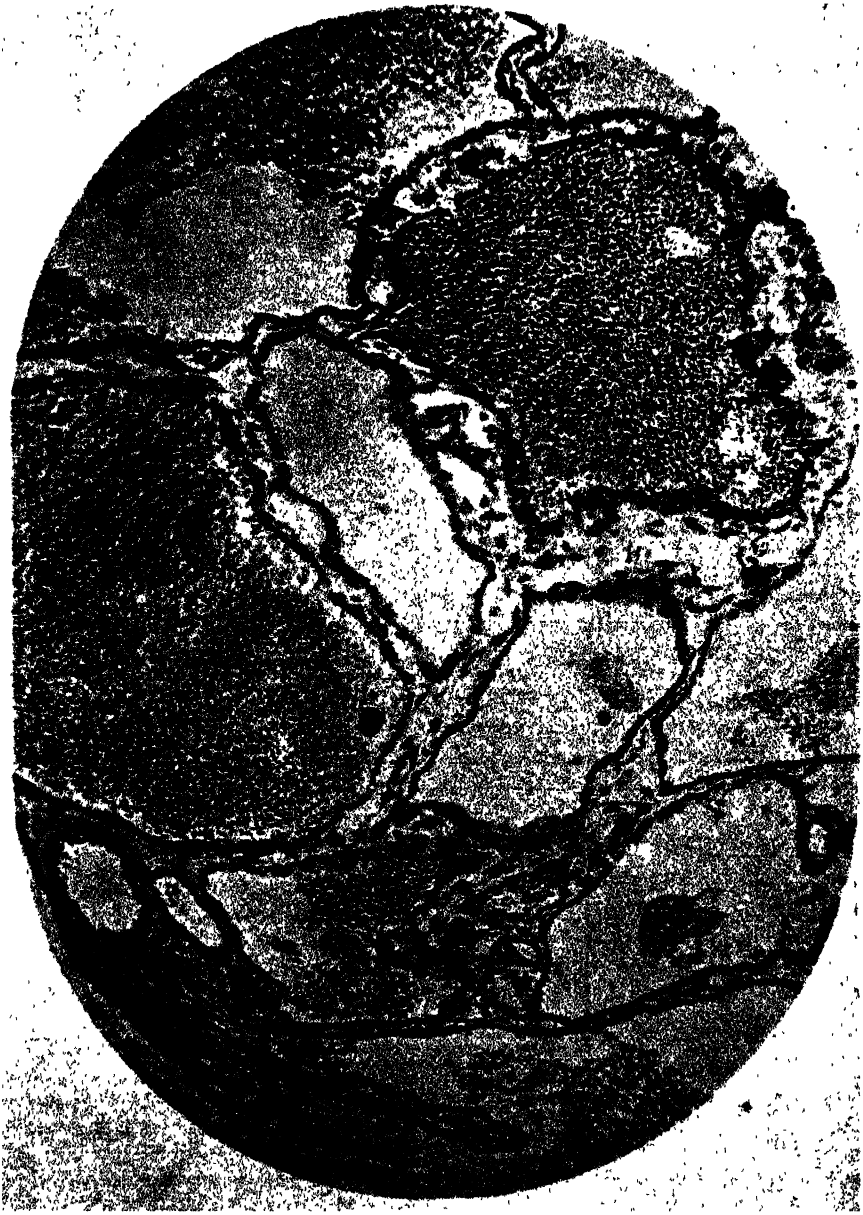

FIG. 94.—Peculiar (pseudo-) haemangiomatoid appearance of parts of a cholangiocellular carcinoma of the dog, the result of haemorrhage into the neoplastic cystic lumina; same tumour as figs. 90 to 93. (15152; 175×).

separated by a larger amount of well differentiated connective tissue than is seen in the portions described under (*a*). (*c*) In still other parts (Fig. 93) there is proliferation of the walls of the neoplastic cysts which become filled to a varying degree with papilliform ingrowths, or sometimes converted into solid masses of cells. (*d*) In some areas (Fig. 94) the contents of the tubules are blood, which completely fills out the cavity and appears to be in free circulation; here the lining cells may remain tall columnar or cuboidal, but often they are flattened, with elongated oval or spindle-shaped nuclei whose nucleoli are inconspicuous, whose pattern is markedly amblychromatic and whose membrane is very delicate. Morphologically, in fact, they could not be distinguished from endothelial cells. Seen alone, these areas could easily lead to a diagnosis of haemangioendothelioma. Mitoses are absent from these flattened cells simulating endothelium. Sometimes all transitions can be followed between these cells and the tall columnar cells in one and the same cyst. In these blood-filled cysts papilliform ingrowths may also occur. The amount of stroma in these areas is small, forming a delicate backing to the spaces, while slightly larger amounts accompany the true blood-vessels. (*e*) In limited parts there is a great increase of the connective-tissue stroma in which the epithelium lies dispersed in thin and elongated cords. (*f*) Lastly a papillomatous type of growth unassociated with cystic dilatation of the tubules may predominate in parts. Here there is a minimum of stroma.

The tumour cells are free from pigment except those flattened endothelial-like elements lining the blood-containing tubules. These are slightly to quite prominently pigmented with haemosiderin, which is also present in macrophages lying in the blood.

It was definitely established that the extension of the tumour in Glisson's capsule is by way of the portal tracts and capsular lymphatics. Frequent examples of invasion of the portal veins are also seen. The M.I.=4·5.

The periportal lymph-nodes contain large nodules obliterating the subcapsular sinus in many places and from here growing invasively into the lymphoid tissue. Lumina are very rudimentary in these secondary growths, which are more of the solid type. For the rest the nodes show extensive haemosiderosis of both the littoral but more especially the "central "(8) histiocytes and much desquamation of the littoral cells as well as a good few neutrophiles in the sinusoids.

The lungs show multiple nodules of similar structure, the lumina being poorly developed. There is a prominent tendency to necrosis. Apart from the secondary tumour nodules (and a severe hyperaemia and oedema—the subject was killed by chloroform on the operating table after exploration had disclosed the cause of the abdominal enlargement and ascites for which it had been sent to be treated) the lung shows, surrounding the secondary tumour foci, a marked chronic catarrhal and proliferative pneumonia which is most interesting on account of the cell changes involved, but would not suitably be discussed in this work. In one of the lung sections in the type collection is marked a beautiful example of apparent amitotic division in a tumour cell.

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(8) This term is used to distinguish those fixed histiocytes of haemopoietic tissues which do not border sinusoidal spaces from the littoral histiocytes, in accordance with my previous suggestion (Jackson, 1934).

Remarks.—This tumour shows the following variations in morphological type, according to common terminology: adenocarcinoma, cystadenocarcinoma, papilliform adenocarcinoma, papilliform cystadenocarcinoma, as well as the peculiar modifications caused by circulation of the blood through the neoplastic tubules where a remarkable false "haemangio-endotheliomatous" appearance results. The close similarity of the tumour cells to bile-duct epithelium in the greater part of the tumour renders the diagnosis easy.

Diagnosis.—Carcinoma cholangiocellulare with metastases to the periportal lymph-nodes and the lungs, in the latter case associated with a peculiar proliferative pneumonia (which is not discussed here).

Summary of the Pathology of Malignant Cholangiocellular Tumours and a comparison with Hepatocellular Tumours.

A comparison of the two malignant epithelial tumour types encountered in the liver can be undertaken here only as regards bovines, the only species in which we have examples of both types. Before undertaking this, we may briefly discuss the canine case by indicating that a close study on a much larger amount of material has been made by Hoogland of these tumours in the domestic carnivores. He indicates that in dogs the tumours are predominantly of a "cyst adenocarcinomatous" type. They are apparently to be regarded as among the common tumours of dogs, although only one case has been encountered in this country. There is no difficulty in diagnosis because not only do the cells closely resemble bile-duct epithelium, but the tubules which they form show a considerable similarity to bile-ducts and the often outspokenly columnar cells with their elongate-oval and proximally situated nuclei cannot be mistaken. This canine type of cholangiocellular tumour may be regarded as the "ideal" type from the viewpoint of the histo-pathological diagnostician.

In the bovine we see, on the contrary, a departure from the ideal and clear-cut type which leads to difficulties in diagnosis, possibly from the standpoint of discrimination between primary and secondary liver tumours, but especially as regards the distinction from hepatocellular carcinoma. While not wishing to deny on the basis of four cases (although this must be considered an exceptionally high number of examples of a tumour considered to be so rare) that there may be cases of transition between bile-duct and liver-cell carcinoma, we must state that in all our cases of liver cancer of oxen we have had no difficulty in making a clear separation into the two classical types. This discrimination is based on the following lines:—

Macroscopically the cholangiocellular tumour has typically a yellowish-white colour and shows scarcely any signs of encapsulation, but on the contrary evidence of active and rapid spread into the surrounding liver tissue. Metastasis to the regional nodes cannot be regarded as an important criterion because this may also be found, although, we think, far less constantly, in the hepatocellular variety. But it is well known that, in general, cholangiocellular tumours early invade the lymph-nodes, while the liver-cell tumours first and for preference form local (haemotogenous) metastases in the liver. Microscopically, the bile-duct tumour is characterised by cells which bear no resemblance to hepatic cells and whose nuclei have the chromatin pattern of the bile-duct epithelium. In liver-cell tumours on the other hand we have seen no examples in which the cells were not instantly recognisable, in spite of their modifications or anaplasia, as of the hepatic type.(⁹). In most of these tumours an outspoken columnar form of the cells with proximal location of the nucleus, which tends often to an elongate-oval shape, is to be seen, at least in parts. In more anaplastic tumours the usual criteria of cell polarity are lost and the nuclei are more uniformly short-oval or spherical in shape. One cannot rely on finding outspoken lumen-formation in the bovine, although when present it is a valuable guide. In such cases the lumina are distinguishable from the (rarer) large lumina of hepatocellular tumours because of the proximal location of the nuclei in the former and a tendency to peripheral condensation and eosinophilia of the cytoplasm. But there is rather a tendency for the cells to form rosettes (as occurs in the hepatocellular tumours). Here again a distinction may be made on the basis of nuclear location and also on the relation to the stroma, as will be mentioned later. (It may be remarked that in the fowl a distinct tendency to polar location of nuclei was seen in hepatocellular carcinoma. This did not occur in relation to lumen-formation, however, but was found in connection with cells in contact with the endothelium of the wider blood-spaces.) The prominence of the collagenous stroma and absence of the universally-penetrating capillary stroma is in great contrast with the liver-cell tumours, in which collagenous trabeculae are rare and often entirely absent and in which each rosette or cell cord is demarcated by a capillary sinusoid. Intranuclear "inclusions" of nucleolar origin were found in two out of four cases of cholangiocellular carcinoma of bovines, never in hepatocellular carcinoma of this species. When the features of cell polarity, columnarity, and lumen-formation are absent, as in two cases (16 and 17) in this material, discrimination may be admitted to be somewhat more difficult. In the one case in question we were, however, fortunate enough to find the features mentioned present in the metastases although absent from the primary tumour. Long before metastatic lesions had been examined, however, we were certain of the cholangiocellular nature of the tumour purely on the basis of cytoplasmic and nuclear characters and on the parenchymal-stromal relationships. These must probably therefore be regarded as the final criteria; and on such has to be based the recognition of a tumour such as described in case 17 where the extreme anaplasia has resulted in the loss of all other characteristics. Lastly, the study of these sections has shown that while the hepatocellular tumour

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(⁹) It is true that among animals we have encountered no case of an extremely anaplastic liver-cell tumour. But even in the frank (diffuse) carcinoma of man, such as may so commonly be seen in natives in this country, anaplastic changes never obscured the liver cell morphology completely.

grows for preference expansively against the surrounding liver tissue and tends especially to penetrate the portal veins, the cholangiocellular tumours have indefinite margins because they spread for preference intralymphatically along the portal tracts; they also, however, have the power to penetrate the portal veins.

B. BENIGN CHOLANGIOCELLULAR TUMOURS.

No cases of adenoma cholangiocellulare occur in the Onderstepoort collection, although there is one case in a bovine (5630) of congenital cystic liver, resembling that described by Joest in his textbook. Adenoma cholangiocellulare is known in all domesticated species but has apparently not been encountered in this country.

EPITHELIAL TUMOURS OF THE THYROID GLAND.

Like the liver, the thyroid gland presents very special problems in respect of the primary tumours which arise from its parenchyma, the cells of both organs being fundamentally endowed with a facile proliferative ability. In the thyroid, a ductless gland, the problems are in one respect simpler, in that we have to deal with proliferations arising from but one type of cell(¹⁰), but this cell type may be most variable in its morphology and in the histological patterns in which it is arranged. In another respect, viz. the difficulty of distinguishing with exactly what kind of proliferation—hyperplastic, benign neoplastic, or malignant—we are confronted in a given case, the difficulties are comparable with and perhaps even more complicated than those that have been discussed in connection with hepatic proliferations.

The chief difficulty of classifying proliferative processes in the thyroid concerns both the distinction between benign and malignant neoplasms (hence the term " malignant adenoma " applied to certain tumours of this organ, which like " malignant adenomas " of the liver are capable of an invasive growth which is nevertheless not reflected by striking anaplastic changes) and the discrimination of localised hyperplastic processes from benign tumours. Some authors are inclined not to speak of adenoma of the thyroid, but of *struma nodosa*. Others apply the term adenoma to any benign proliferative lesion, however minute, which is considered to exhibit the quality of autonomous growth.

Strumas [non-inflammatory enlargements of the thyroid gland, from which are usually excluded malignant lesions(¹¹)] are divided into *S. diffusa* and *S. nodosa*. It is with the latter that we are here concerned. This lesion is usually described as single or multiple circumscribed nodules which are enclosed by a connective-tissue capsule, and by nearly all authors this encapsulation is stressed as an essential feature. No provision is usually made for nodules which, while lacking encapsulation, may either be well circumscribed or

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(¹⁰) Cysts of the thyroid, considered to arise as persistent remnants of the thyroglossal duct, are extremely common in sheep in this country and have been studied by Thomas (1930).

(¹¹) Yet some authors are willing to speak of malignant strumas.

more indistinctly demarcated from the surrounding tissue; although Wegelin (1926) mentions a nodular hyperplasia of the thyroid under which term are described circumscribed but not sharply demarcated (i.e. unencapsulated) nodules which are of the colloid type. These, it is remarked, are intermediate between diffuse struma and the true (encapsulated) adenomas and often cannot be distinguished with certainty from the early stage of an adenoma. I find, however, no mention in human pathology of nodules having the above features but which histologically are of the " parenchymatous " (solid or " foetal " type) and which, as will be seen, are commonly encountered in the horse. On general principles, however, it would seem reasonable that if from " colloid " adenomas are distinguished nodular hyperplasias of colloid type, then, when need arises, one should also distinguish from " parenchymatous " adenomas, nodular hyperplasias of " parenchymatous " type which are characterised by lack of encapsulation and by less distinct circumscription.

The typical thyroid adenoma (synonymous therefore with *S. nodosa*) as described both by Trautmann (1924) and in Kitt's (1927) textbook of veterinary pathology (*Bd.* III), are considered to be demarcated by a capsule from the surrounding tissue. These authors are of course following the general principle, as laid down by Borst (1902) that the presence of a capsule is an essential distinguishing feature between localised hyperplasia and adenoma. Wegelin mentions, however, that there is no hard and fast line between hyperplasias and true tumours of the thyroid and himself pictures an adenoma which is " *noch nicht völlig abgegrenzt* "; he conceives the genesis of the capsule in the following way:—The *Adenomkeime* (12) which still lie within the parenchyma of a secondary lobule of the gland naturally lack a capsule. When the proliferating epithelium has progressed to reach the connective-tissue septa which surround the gland lobule, the pre-existing connective-tissue provides a capsule which is at first delicate . . . but which with continued growth of the adenoma becomes augmented, partly owing to its response to the increasing tension to which it is subjected, but still more owing to the atrophy and fibrosis of the now insufficiently nourished adjoining thyroid tissue.

Schlotthauer (1931), who has described in some detail these lesions of the equine thyroid, mentions that of 34 specimens, 4 were unencapsulated, while of the rest some were only partially encapsulated. However, he uses the term adenoma in every case. The wisdom of this is open to question, but it has at least the merit of laying stress on a conclusion with which no one examining such lesions can fail to agree, viz. that directly from minute (even microscopic) unencapsulated hyperplasias develop large and well encapsulated lesions fully deserving the name adenoma. One has therefore to face the dilemma that although a single and continuous biological process may be in question, the attempt to apply a single term to its various phases must result in one of two incongruities: either minute, unencapsulated proliferations, of which it is impossible to say with certainty that they have attained independence from the surrounding tissue, are misleadingly described as adenomas; or, on the other hand, larger, fully encapsulated lesions, clearly growing *aus sich heraus* have to receive the equally unsuitable designation of hyperplasias. Thus, while we may succeed in indicating the fundamental identity of the different types as phases of the same process, the attempt to unify nomenclature not only leads to a confusion of the general principles whereby the neoplastic is distinguished from the non-neoplastic, but actually results in creating a false picture of what we are attempting to describe.

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(12) The exact nomenclature to be applied to the pre-adenomatous lesion or the very young adenoma is not indicated.

It is not profitable to pursue further a discussion of these difficulties, already so familiar to pathologists in many other connections. There is at present no real escape from such dilemmas which, although incapable of solution in terms of simple nomenclature, should yet be kept in mind because of the significance of the principles which underlie them.

Another difficulty in the diagnosis of thyroid neoplasms concerns more especially the malignant tumours and consists in the fact that the cells of proliferating thyroid epithelium may assume spindle-shapes, leading to a confusion with sarcoma. This difficulty is familiar to human pathologists (see, for example, Smith, 1930) and it is still to-day a vexed question whether primary sarcoma of the thyroid occurs or whether all tumours diagnosed as such are "pseudosarcomatous" carcinomas. I have not found this difficulty referred to in the veterinary literature.

The Onderstepoort collection is poor in thyroid neoplasms, a circumstance for which the limited occurrence of strumas in this country is probably partly responsible. In dogs, in some parts of the world, goitre as well as thyroid carcinoma is relatively common (Bartlett, 1914, and Schlotthauer, McKennedy and Caylor, 1930, in America; Huguenin, in Switzerland); and the latter is considered to bear an aetiological relationship to the former. In this country, however, neoplasms of the thyroid have been encountered only in horses. In this species Schlotthauer (1931) in America and several others before him in Europe have indicated the extremely frequent occurrence of benign tumours of the thyroid (e.g. 37 per cent. of animals). And it is probable that the presence in our collection of only 6 specimens of localised non-malignant proliferations of the thyroid of horses does not reflect a low incidence of such lesions in this country: such changes are both likely to be overlooked at autopsy (many being invisible until the thyroid is incised and the cut surface closely scrutinized, and even then possibly being mistaken for embedded parathyroids) or are often not considered worth submitting as specimens for microscopic examination.

Since the benign thyroid tumours of the horse have already been closely described, especially by Schlotthauer, I do not propose to burden this text with any detailed description. Suffice it to say that among the Onderstepoort cases occur both fully encapsulated and partially encapsulated lesions; while some which entirely lack a capsule and further are poorly circumscribed and do not exert pressure on the neighbouring tissue have not been included as neoplasms. In structure, the tumours vary considerably, being either predominantly of what is familiarly known as the " parenchymatous " or " foetal " (13) type, or of the colloid type; often there is a more or less equal admixture of both growth-modes (" foetal and colloid " adenoma). Variation occurs not only in one and the same nodule, but especially in different nodules in the same gland, and multiplicity is a very usual feature. In one case (Equine, 9616) an erroneous diagnosis had been made of spindle-celled sarcoma! The small lesion in question is, however, distinctly of benign structure, but the epithelial cells, assuming a spindle shape, simulate fibroblasts to a remarkable degree. An intercellular stroma is absent, however. While one expects the cells of thyroid carcinoma often to be thus modified, I find no description of such a modification of the cells of a benign struma.

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(13) The theory of origin of " foetal " adenoma from embryonic tissue (Wölfler) has in more recent times gone greatly out of favour and the term retains, for the most reliable authorities at the present time, nothing more than a descriptive significance.

CHAPTER V.

Thymoma.

In accordance with the consensus of modern opinion, the term thymoma is here used to indicate neoplasms which arise from the cellular elements (whatever their morphology) which constitute the actual parenchyma of the thymus, as distinct from those of the stroma and of infiltrating cells not proper to the organ itself. In spite of the criticism which has been levelled at the introduction of this term, so long as the histogenesis of the thymus remains doubtful it is obviously unwise to apply to tumours of the thymic parenchyma a classification based on histogenetic assumptions. Symmers (1932) objects strenuously to the designation thymoma, saying: " it is difficult to understand why one should use the term ' thymoma ' as a designation for lymphosarcoma of the thymus, while retaining the appellation ' lymphosarcoma ' for tumours of identical nature in other parts of the body. As yet, so far as I am aware, no such word has been used as ' intestinoma ' . . . nor ' gastrimoma ' . . . the practice of naming tumours after the organs in which they arise is a philologic desecration. Thus ' hypernephroma ', is meaningless except as the designation for a tumour somewhere ' above ' the kidney . . . ' hepatoma ' conveys no conception of the cell derivation of the several tumours of the liver, ' ovarioma ' does not serve to clarify our knowledge of the cell origin of tumours of the ovary ".

In this criticism Symmers appears to miss the whole reason why the term thymoma has come into use, and his comparisons with tumours of organs like the bowel and stomach, etc., whose histogenesis is not in doubt, are quite beside the point. As Margolis (1931) has well said: " A correct anatomic classification of thymic neoplasms presupposes unequivocal proof of the sources of the thymic cells from which these tumours arise. In the absence of conclusive knowledge regarding the histogenesis of all the constituents of the thymus, attempts at detailed classification of tumours of its parenchyma must perforce lead to inaccuracies. It appears inconsistent to admit lack of knowledge of the histogenesis of the normal thymus and yet to proceed with a dogmatic sub-division of tumours of the thymic *parenchyma* into carcinomas and lymphosarcomas, implying an origin on the one hand from epithelial structures, and on the other from ' lymphocytic ' elements. When final conclusions concerning the origin of the various elements of the thymic parenchyma become available, such a classification may be shown to be entirely incorrect, in which case it would have served only to increase the overburdening confusion that already exists regarding many aspects of our knowledge of the thymus. Any classification of tumours arising from the thymic parenchyma, if it is to serve a useful purpose, should imply clearly the lack of definite knowledge regarding their source, thus avoiding confusion and stimulating interest in studies which may throw further light on this problem."

Margolis is wise in maintaining a reserved attitude in regard to our knowledge of thymic histogenesis. The literature on this subject is most extensive and authorities are still divided in their views. It may here be briefly recalled that while fairly general agreement has been reached regarding the entodermal origin of the supporting recticulum-cells, and while the Hassall's corpuscles [notwithstanding the revival by Jordan and Horsley (1927) of the old view of Afanassiew (1877) that they are of vascular endothelial derivation] are still generally reckoned (e.g. Hammar, 1909, Jaffe and Plowska, 1925) to be derived from these reticulum-cells, the greatest controversy still persists regarding the nature and origin of the small round cells (" thymocytes ", " thymic lymphocytes ") and great doubt has been cast on the views of Hammar (1905), Maximow (1909), and Danchakoff (1916), who held the " pseudomorphosis " theory—that the cells in question are immigrant elements (viz. lymphocytes) from the mesenchyme surrounding the epithelial *Anlage*—by a number of earlier and later workers (Prennant, 1894, Bell, 1906, Stöhr, 1906, Dustin, 1911, Gottesman and Jaffe, 1926) who urge the " transformation theory ": this postulates the transformation of epithelial elements into cells which, although morphologically resembling lymphocytes, must be rigidly distinguished therefrom in virtue of a non-mesenchymal origin and a difference in function and potentialities. The subject has been extensively reviewed by Badertscher (1915) who himself, however, adheres to the migration theory.

In the light of this controversy it is then easy to see the difficulties that beset classification. If all the parenchymatous elements (reticulum cells, Hassall's corpuscles, and " thymocytes ") are of epithelial origin, only one kind of malignant tumour, viz. carcinoma, can arise from thymic parenchyma. On the other hand, if the " thymocytes " are true lymphocytes, the designation " lymphosarcoma " for some of the thymic tumours would be correct, while if the endothelial origin of the Hassall's corpuscles be accepted, tumours arising therefrom would not be thymic parenchymal neoplasms at all, and would have to be classified as endotheliomas of stromal origin along with the fibroblastic sarcomas, etc., that may similarly arise.

Especially may objections be raised to the proposal to designate as lymphosarcomas tumours of round cells in the thymus, and on the following grounds:—

(1) The lymphocytic nature of the thymocytes cannot be regarded as established with certainty. This is especially in doubt because of their apparent origin from regenerative reticulum-cells in thymic transplants (Gottesman and Jaffe, 1926) and because of the non-participation of the thymocytes in lymphatic leucaemia (Margolis 1930). In this connection Margolis remarks that " on *a priori* grounds it may be assumed that if the small thymic cells are true lymphocytes, having not only a morphological resemblance to blood lymphocytes, but also a common histogenetic relationship to them, there would occur in lymphatic leukaemia hyperplasia of the thymus gland step by step with hyperplasia of the lymphatic structures elsewhere in the body ". This he finds not to be the case.

(2) Between tumours composed of round cells (" lymphosarcomas ") and those of epithelial reticulum-cells (carcinomas) there are intergrades in which the reticulum-cells are intimately admixed with thymocyte-like elements. For these the undesirable term " lymphoepithelioma " has been introduced (e.g. by Nathan 1929). This serves no further to clarify the histogenesis, and in strict defence of this term the thymic dualists would have to postulate a carcinogenic stimulus operating on two different types of cell simultaneously (see Chapter X).

(3) Some (e.g. Ewing), while using the term lymphosarcoma, admit (*a*) that the round-celled tumours concerned actually differ from the true lymphosarcomas of lymphatic tissue and (*b*) that the source of the tumour is actually the reticulum cell, " the lymphocytes being largely passive ".

I am not here urging the non-lymphocytic nature of the thymocyte, nor would this be the place for such a discussion, but am merely pointing out the need to refrain from any sub-classification of thymic tumours which would imply as yet unproven assumptions of thymic histogenesis.

Occurrence.—In human pathology, tumours of the thymus are considered rare and are reported. In the veterinary literature one finds extremely scanty information regarding them. Feldman (1932) does not mention thymoma, and apparently encountered in America no case of thymic neoplasm among his extensive collection of specimens numbering approximately 600. But it appears quite likely that his two cases of " pleural mesothelioma " of bovines were in reality thymomas, the photomicrographs strongly suggesting such an interpretation, especially the duality of cell types and the squamous-like epithelium which is mentioned. Trautmann (1924), in Joest's textbook, devotes a couple of pages to the consideration of all tumours of the thymus. Apart from the non-parenchymal neoplasms he indicates that only in the cases of Schmidt (1921) and Wyssmann (1911), in a bovine and a pig respectively, diagnosed as round-cell sarcomas, was a thymic origin clearly established. The other cases mentioned concern either stromal tumours (fibroblastic sarcomas), " lymphosarcomas " in which the description does not enable one with certainty to know if the disease was primary in the thymus (cf. lymphosarcomas arising in the mediastinal lymph-nodes), possible cases in horses described as " carcinomas " but of which no detailed descriptions were given, and a case reported by Joest himself (1912) of a tumour histologically of a mixed character found on the heart-base of a dog, but which he was inclined to designate as a " thymic adenoma " or thymoma mainly because he could not explain its origin and location by any other hypothesis (Hassall's corpuscles were not present). In this connection I must refer to my own investigations on the heart-base tumours of the dog, which indicate that tumours of distinctly epithelial appearance arising in this situation have an altogether different histogenesis, not requiring to find their explanation in an origin from some adjacent organ.

I have not been able to trace any further reports of thymic neoplasms in domesticated animals since the date of Trautmann's review and one must conclude therefore that only two authenticated cases of parenchymal thymic neoplasms have been reported, that in both these cases there was nothing of carcinomatous structure in the tumours, and that apart from those in the bovine and the pig no undoubted cases at all are recorded.

It is, therefore, perhaps surprising that from the Onderstepoort material one is able to describe no fewer than seven thymomas, in all of which I am completely satisfied of the correctness of the diagnosis. Three of the cases concern bovines, three were found in sheep, in which species thymoma has not previously been reported, and the seventh case occurred in a goat, in which species this tumour is likewise unrecorded. The cases will be described in full:—

Case 1 (*Bovine*, 14726).

The subject was (¹) a cross-bred Fries ox, ten years of age, in good condition. The animal lost power in its limbs, could rise on the fore-feet only, later developed dysphagia being able to swallow fluids only, and was apparently in great pain. It had to be destroyed five days after the first symptoms were noticed. On post-mortem a growth was found " just inside the thorax, involving the oesophagus ". An enlargement was visible externally.

A flattened discoidal piece of creamy coloured tissue was submitted for diagnosis. It measured 8 × 6 × 1·5 cm., but apparently represented only a portion of the entire tumour. On one surface it was covered by a thin connective-tissue capsule, while the opposite surface (a cut surface) was honey-combed by innumerable polygonal cavities containing a whitish jelly (formalin-fixed specimen—contents coagulated).

Microscopically (Figs. 95 and 96), the sections show that (on the intact side) the tumour is covered by a fairly thin collagenous connective-tissue capsule well supplied by blood-vessels and lymphatics. In parts this capsule itself is infiltrated by the neoplastic cells. There is also in parts a leucocytic infiltration and in some of the capsular lymphatics large numbers of cocci are present. From the capsule proceed inwards only occasional collagenous trabeculae and for the most part the stroma of the tumour is formed solely by thin-walled blood-vessels, of which there is a generous supply. The parenchyma is composed of the pleomorphic cells to be described, lying between which are small round cells having trachychromatic and pachychromatic, rounded or slightly angular nuclei, i.e. the morphology of thymocytes or small lymphocytes. The chief cells present a varying appearance and this pleomorphism appears to be due partly to growth pressure and partly to actual varying degrees of differentiation. Regarding their arrangement, the most prominent feature is their occurrence in whorls (Fig. 95) which have the following appearance. The cells in the central part of the whorl lie somewhat irregularly arranged and possess a relatively

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(¹) According to the sender, the Government Veterinary Officer, Grahamstown.

large amount of faintly staining cytoplasm whose border is indistinct. The nuclei vary much in size and may be crowded together with their borders touching or may be more widely separated. These nuclei are variable in shape, oval to rounded. They have a rather sharply defined membrane and are decidedly vesicular in appearance. They may show inconspicuous nucleoli. Often there is hyperchromatism and the membrane appears thickened on account of peripheral condensation of the chromatin, either in the form of several wedge-shaped masses with their bases lying against the membrane or as two masses at opposite ends of the nucleus, giving the latter a striking bipolar or "capped" appearance.

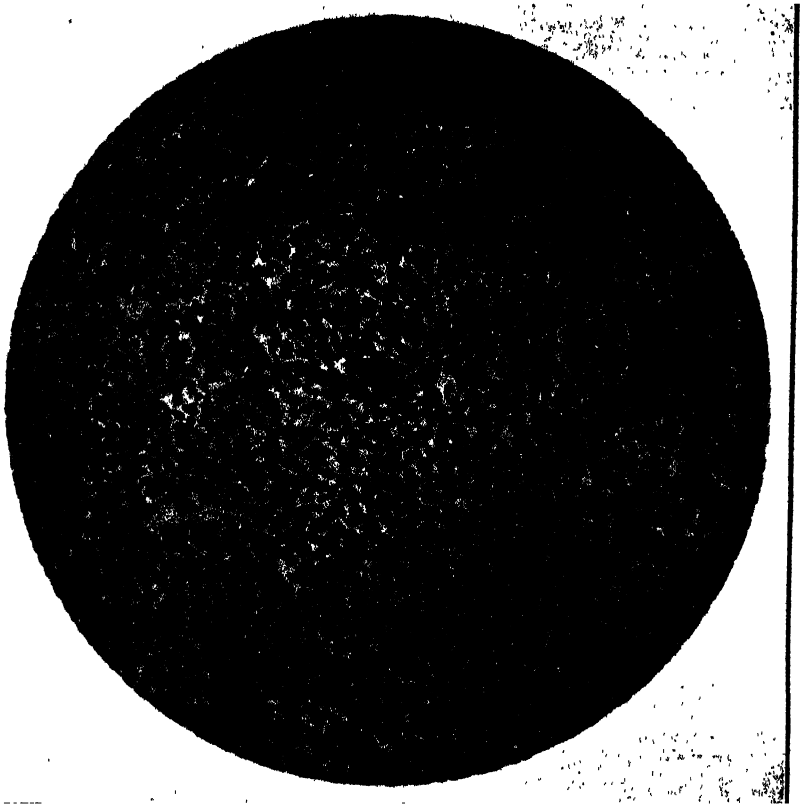

FIG. 95.—Thymoma of the bovine: Duality of the cell types and tendency to arrangement in whorls. (14726; 240×).

Around this central portion, and without demarcation therefrom, the cells are arranged in concentric whorl formation, becoming increasingly spindle-shaped towards the periphery. The cytoplasm of these cells is smaller in amount. The nuclei vary from elongated oval to long cigar or spindle shapes. Apart from this lateral compression the nuclei are similar to those of the centrally placed cells.

At the periphery of the whorls, the cells pass over insensibly to a diffuse type of growth in which they are arranged in long, ill-defined strands running in all directions and composed of spindle-shaped elements arranged with their long axes parallel to one another or of cells which are more widely separated and irregular in shape, with indistinct cytoplasmic borders, and rounded or oval nuclei.

While round cells occur in varying numbers among these chief cells, whatever their arrangement may be, yet the whorls and the strands of spindle cells are relatively, and often entirely, free therefrom. The round cells lie in greatest number among the more irregularly and diffusely arranged chief cells. In large parts of the tumour this latter pattern is the only one seen, the whorls being absent. In such areas there are more lightly and more darkly stained fields depending on the density of aggregation of the round cells, which in some places are actually more numerous than the chief cells, but this is not usual. Although this alteration of light and dark areas occurs without definite pattern, the appearance produced is very reminiscent of cortical and medullary areas of the thymic lobules, although of course there are no septa demarcating lobules.

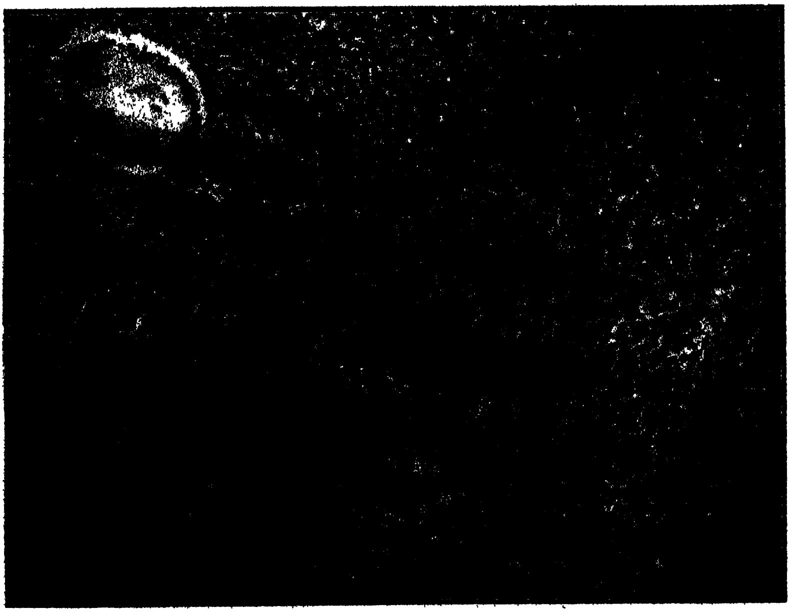

Fig. 96.—Another portion of the bovine thymoma illustrated in fig. 95: Formation of Hassall's corpuscles (right) and of cysts (above, left). (14726; 120×).

In many places (Fig. 96) the cells become greatly changed in appearance: the cytoplasm is markedly increased in amount, although still faintly staining and syncytial in nature, and the nuclei are increasingly vesicular and often attain twice the size of those previously described. Thus are formed large, irregular sheets and strands of cytoplasm with widely separated nuclei. Among the cells of these sheets there are some which show pronounced degeneration. The cytoplasm becomes more acidophilic and of a hyaline appearance, comes to contain vacuoles and inclusions, and the chromatin of the nucleus becomes arranged in fine dust-like particles, the nuclei ultimately undergoing lysis, with a surrounding concentric striation of the cytoplasm. Many of the structures so formed are quite clearly of the nature of Hassall's corpuscles (Fig. 96). The same degenerative changes may overtake individual cells in other parts of the neoplasm.

Cysts of two types occur:—(1) In parts, cysts of this type occupy a considerable amount of the tumour tissue. They are large, irregularly polyhedral cavities (seen macroscopically, *v. supra*) lined by cells of the type which take part in the formation of the " Hassall's corpuscles ", and having no backing of connective tissue whatever. In other words they are merely spaces in the tumour at the edges of which the chief cells become larger and arranged to form an irregular lining. These cysts contain a serous material in which are found round cells, desquamated lining cells, and strands of fibrin, or sometimes a fair number of erythrocytes. (2) Comparatively infrequent are smaller tubules or cysts of circular outline and lined by cells of unmistakably epithelial appearance (Fig. 96). The cells are columnar in shape and have ill-defined contiguous borders and a condensation of the cytoplasm at the free (distal) border which causes a thin reddish line to appear in haemalum-eosin-stained sections. Their nuclei are spherical to oval. There is no basement membrane or sub-epithelial connective-tissue layer, the cell cytoplasm being, at the base of the cell in continuity with that of the diffusely growing chief cells in the immediate vicinity, although in some sections such continuity is obscured by a retraction of the surrounding tissue from the tubular lining, leaving an artificially-produced space. The nature of the nuclei of these columnar cells is similar to that of those of the other varieties of the chief cell. These cysts contain a serous fluid and occasional small round cells and pigmented macrophages. Occasionally the lining cells are much flattened, simulating an endothelium.

A study of sections stained with Mallory's fibrillar stains shows that in general a fibrous reticulum is absent. In the degenerating large cells forming Hassall's corpuscle-like structures the phosphotungstic-acid-haematoxylin method reveals prominent, blue-staining, intracellular fibrils and granules. A delicate, intercellular reticulum may be shown up by the triple stain in parts where the round cells are closely aggregated (probably associated with the adventitia of blood-vessels), but usually disappears completely in the purely reticulum-cell portions of the growth, e.g. in the whorls.

Mitoses are only found in the tumour after prolonged searching.

Remarks.—This tumour had previously been diagnosed (routinely) as endothelioma, no information having been supplied regarding its situation. The nature of the neoplastic cells and the prominence of whorls make this interpretation quite easy to understand. On seeing the preparation, however, I was struck by the syncytial nature of the neoplastic parenchyma and especially by the

Hassall's corpuscle-like structures and the epithelial-lined cysts, and succeeded on enquiry in eliciting from the sender an admission that the growth occurred in the thoracic inlet and cranial mediastinum as described above.

The thymic origin of this tumour is clear both from its location and from the histology. It is to be regarded as arising from thymic reticulum (epithelial) cells and corresponds to the tumours of the human thymus for which the designation carcinoma is often used. The association of the small round cells with the chief cells in such cases has led German authors to the designation "lympho-epithelioma", but such a term is objectionable because (*a*) "lymphocyte" is in any case a term which it is inadvisable to use when referring to thymocytes, (*b*) the round cells do not appear necessarily to represent an integral part of the tumour, apparently behaving passively, and (*c*) the term would suggest a mixed tumour of dual histogenesis, a conception which can find little support from a study of such growths, and which indeed, we scarcely believe that those who use it intend to imply. There is, further, grave objection to the use of the term carcinoma for such tumours in the present state of our knowledge, for as Margolis has pointed out, this is likely to be construed as implying the probability that there is more than one thymic parenchymal neoplasm, viz. carcinoma and lymphosarcoma, and that the thymus has a dual histogenesis. For these reasons the term thymoma is retained in diagnosing the present case as well as the two following ones.

Case 2 (*Bovine*, 5966).

The subject was also a bovine, of which no details are available.

Macroscopically, the museum specimen (Fig. 97) consists of a bulky tumour lying in the cranial mediastinum ventral to the apical lobe of the right lung, which it displaces dorsally. The main mass of the tumour measures 14 cm. in diameter. It is laterally compressed and for the most part limited by the mediastinal pleura, which is firmly adherent to the apex of the lung. There appears to be no actual invasion of the pulmonary tissue at any point. The mass has a whitish colour and it shows some tendency to lobation, very irregular tracts of tissue being demarcated by loose connective-tissue septa. It is traversed by a few blood-vessels of venous type and has a soft, friable consistency, resembling lymphoid tissue. Ventrally there is extensive penetration of the capsule. The pericardiac pleura in its lower part and the pulmonary pleura of the apical lobe of the lung show multiple, broadly attached, raised nodules of the same tissue varying in diameter from 2 mm. to 2·5 cm. and one still larger mass, 7 cm. in diameter and apparently composed of confluent nodules, lies partially on and partially invading the mediastinal pleura at its junction with and immediately caudal to the pericardiac pleura. The ventral border of the lung is adherent to this mass by strong fibrous bands.

The structure as seen in many of the sections is somewhat misleading. On casual examination one simply sees closely packed masses of small round cells having the morphology of small lymphocytes (thymocytes) and one is at first glance inclined to think of a lymphocytic or " round-celled " tumour. On examination of the same sections stained by Mallory's triple stain, suspicion is aroused because these round cells are seen not to be supported by a fibrillar reticulum(²); such reticulum is confined to the blood-vessel adventitiae from which it may penetrate for only a very limited distance between the cells. This finding leads to a closer scrutiny (for of course it is a general rule that non-sessile cells in tissues be they normal or neoplastic, require support). It is then seen that the small round cells are supported by larger and paler elements, which in most parts of the tumour are, however, almost completely obscured (cf. the cortical portion of the normal thymic lobule) by the densely aggregated round cells. These pale elements can be well studied only in certain parts of the tumour, where they are seen to be poorly outlined, irregularly shaped, and branching cells which form small sheets or tracts in which the cytoplasm of the individual elements is not clearly demarcated, in which there is relatively little or no admixture of round cells, and with which is continuous the branching cellular reticulum forming the support for the dense masses of round cells. These large cells may measure up to 30μ in diameter. They have

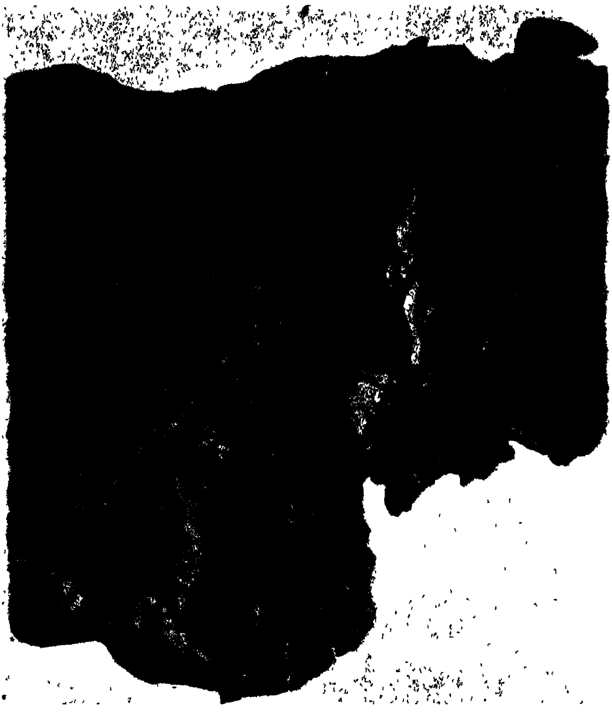

FIG. 97.—Gross appearance of thymoma of the ox: Tumour situated in the cardiac mediastinum (right) displacing upwards the apical lobe of the lung; secondary nodules on the pericardiac pleura (centre, below) and on the pulmonary pleura (to left of and above centre). (5966; 1/3×).

(²) With Mallory's stain, the cell borders, often more deeply stained, must not be mistaken for a reticulum.

large, pale, oval nuclei showing considerable variation in size and shape, often measuring some 18μ in diameter (smaller ones measuring *ca.* 10μ are also to be seen). The nuclear membrane may be thickened in parts and often shows coarse indentations or serrations. The chromatin network is very inconspicuous and, indeed, not at all visible in the majority of the cells. The cytoplasm is rather large in amount and may be conspicuously vacuolated. In many cases several nuclei lie closely aggregated in a mass of cytoplasm in which no demarcation of individual cells can be discerned. Scattered eosinophiles are present throughout.

No mitoses are seen in the small round cells, while among the large supporting cells mitotic figures can be demonstrated only by prolonged searching. The very low mitotic index was not worth recording. No evidence of transitions between supporting cells and round cells was obtained.

Remarks.—This tumour had erroneously been diagnosed as a " round-celled sarcoma ". But the location in the cranial mediastinum, the absence of intercellular reticulum, the limited malignancy (as shown by the tendency to encapsulation, the low mitotic index and absence of true metastasis), the presence of the characteristic supporting cells, which lack association with reticulum fibres, which are also arranged in sheets, and among which here again the round cells, however much they may dominate the picture, appear yet to play a passive rôle, are all quite characteristic of tumours of thymic origin. Although the typical Hassall's corpuscle-like moieties are not seen, there is here also no hesitation in identifying the tumour as thymoma. The discrete nodules on the pulmonary and pericardiac pleurae are interpreted as transcoelomic implantations and are to be correlated with the capsular penetration observed in the primary tumour.

Case 3 (*Bovine*, 6467).

No details are available regarding the subject of this specimen(³). It consists of fragments only of a soft-textured neoplasm which is encapsulated beneath a serous membrane (pleura).

Microscopically, the neoplastic tissue is enclosed by a well-developed collagenous connective-tissue capsule (corresponding to the thickened subserosa), the outer surface of which is covered by (pleural) mesothelium. In places the capsule is infiltrated by the tumour parenchyma to a limited extent. From the capsule occasional thick strands of connective tissue course through the tumour, the stroma being otherwise almost exclusively formed by small blood-vessels, which are present in rather large numbers. The tumour parenchyma consists of a diffuse arrangement of ill-defined cells with pale staining nuclei. They are apparently arranged as a syncytium and between them occur very variable numbers of small round elements having the morphology of small lymphocytes. In many places the latter are so densely arranged as almost to obscure the pale supporting cells, in other parts the supporting elements predominate. The cytoplasm of the latter is not easily studied: it stains very palely with haemalum-eosin, is non-granular, and

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(³) Received from the G.V.O., Durban.

appears to assume ill-defined spindle and stellate shapes. The nuclei are characterised by pleomorphism and by extreme amblychromasia. In general they are large, but vary from *ca.* 5·5μ to 13·5μ in longest diameter; most of them exceed 10μ. They vary greatly in shape from oval and spindle forms to kidney and bean forms; not a few are highly irregular, the thin and sharply-defined nuclear membrane presenting serrations and angularities. Twisted dumb-bell shapes suggestive of meiosis are also to be seen. The nuclei are very poor in chromatin, which exists as a scarcely visible network or as extremely fine granules. In many of them no nucleolus is identifiable, but in the majority one or two inconspicuous nucleoli are seen (n : N = 1 : 50 to 1 : 25). Larger nucleoli (n : N = 1 : 9) may be found in certain small, non-sessile, rounded cells which still have amblychromatic nuclei and which (leaving aside theoretical implications and judging merely on the morphological appearances) could well be described as transitional between the reticulum cell type and the lymphocyte-like type. So much for the size of nucleoli which are unaltered in staining qualities and which are readily recognisable as such. But globular intranuclear ("inclusion") bodies are of fairly frequent occurrence in the supporting cells and reach considerable dimensions. They are identical with those described elsewhere in this work, and doubtless also represent altered nucleoli. They are sharply outlined, hyaline bodies, rounded to oval in shape and situated centrally in the nucleus. They vary greatly in size, reaching a diameter of 7·5μ. When fully developed they do not take a stain, or stain a very faint pink with haemalum-eosin. Stages intermediate between these bodies and "normal" nucleoli can be recognised. Such an altered nucleolus may be found along with a "normal" nucleolus in the same nucleus. Including these bodies in the consideration of the n : N ratio one obtains a figure of as much as 1 : 2·5.

The cells described are in continuity with concentrically arranged elements of the same general type which surround one or more central degenerated cells. These bodies are often the subject of neutrophile infiltration and in all respects resemble the concentric corpuscles of Hassall; but they are of much less frequent occurrence than in thymus tissue and so are easily overlooked. They are strongly acidophilic and present concentric lamellation. The nuclei of the degenerate elements are pycnotic, those of the surrounding concentric elements are somewhat enlarged and hyperchromatic, being "dusted" with comparatively coarse granules of chromatin. Individual elements undergoing similar changes and having a condensed, strongly eosinophilic cytoplasm may also occasionally be encountered.

Eosinophilic myelocytes, mature eosinophiles, and all intermediate stages are found scattered among the other elements in inconstant but often considerable numbers. The myelocytes, especially in their earliest stages (promyelocytes) are often so closely related to the reticulum cells as to suggest the possibility of a direct transformation of the latter into the former. This possibility had always been borne in mind in the examination of the other cases of thymoma described in this work, but no finality was arrived at. It seemed that in the tumour under discussion, an opportunity of proof was offered in view of the occurrence of the hyalinised nucleoli in the tumour cells. If such could also be demonstrated in the eosinophile granule-containing elements, valuable evidence of the suspected transformation would be provided. However, in spite of the closest scrutiny, it was not possible to identify such bodies in the nuclei of granule-containing cells, although many of the eosinophilic precursors could not be distinguished from the tumour cells on any basis other than that of the presence of granules in their cytoplasm.

As has already been mentioned, the appearances seen in this tumour are also consistent with the transformation of the reticulum type of tumour cells into the thymocyte type. But here also it seems better to keep an open mind regarding this possibility.

The reticular intercellular stroma in this tumour is confined mainly to the vicinity of the blood-vessels, and in places where capillaries are numerous a fairly continuous fibrillar stroma is to be seen between the neoplastic cells; but here, as elsewhere (where blood-vessels are less numerous), there appears to be no special association of the fibrils with the neoplastic cells, and it was concluded that these cells do not participate in the formation of fibrils(4).

In parts of the tumour there is extensive necrosis and fibrosis. Blood-cells may be seen in direct contact with the neoplastic cells in places. The mitotic index is nil.

Remarks.—No details of the autopsy appearances are available in this case, which is therefore useful in illustrating with what degree of certainty thymoma may be recognised in the absence of such information, a point which is often of great practical importance in veterinary pathological routine, in which so frequently accurate information does not accompany the specimens submitted. From the circumstance that the tumour tissue is encapsulated beneath the pleura, one can deduce with reasonable certainty that it occupied the mediastinum. The histologic and cytologic details—tendency to invade the capsule, the structure of branching reticulum-like neoplastic cells (not especially associated with fibrous reticulum) supporting small round cells which appear to be largely passive in their behaviour, the presence of eosinophiles and their precursors, and finally the Hassall's corpuscles—all are typical of thymoma. Previously, an erroneous diagnosis of " round cell sarcoma " had been made.

Case 4 (*Bovine*, 12785).

The specimen, which represents the half of a tumour found during the dressing of the carcass of an ox " between the heart and the bifurcation of the trachea ", is an ovoid mass measuring about 15 cm. in length. It is encapsulated beneath the mediastinal pleura. On section a system of coarse bands of dense, white fibrous tissue is conspicuous; these septa vary from 3 mm. to as much as 1 cm. in width. They demarcate the soft, yellowish-white parenchyma into irregular areas measuring from 1 to 4 cm. in diameter. Reddish discolorations (haemorrhages) are frequent in the tissue and may measure up to 1 cm. in diameter.

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(4) Note that with reference to the reticulum in normal thymic tissue the position is generally regarded as being the same as is described in this tumour.

On microscopic examination is seen a system of coarse, acellular trabeculae of hyaline fibrous tissue with delicate secondary septa in which the smaller blood-vessels are supported by reticular connective tissue only. The parenchyma consists of palely staining cells with ill-defined cytoplasmic boundaries and oval to spindle-shaped nuclei. The latter are amblychromatic and have inconspicuous nucleoli, although hyaline intranuclear bodies (presumably of nucleolar origin) are of frequent occurrence. These cells, although arranged as a syncytium, are not definitely or regularly associated with a fibrous reticulum. Among them occur a variable but usually small number of round cells having the structure of small lymphocytes. There are many areas of necrobiosis, haemorrhage, and calcification. Both the capsule and the coarse bands of the stroma are often partially invaded by the parenchymal elements. No Hassall's corpuscles were seen. Eosinophiles are absent. The M.I. is 0.

Remark.—An erroneous diagnosis of spindle-celled sarcoma had been made.

Diagnosis.—Thymoma.

FIG. 98.—Thymoma in the sheep: A massive tumour of the precardiac mediastinum, extending backwards to the cardiac region; note the displacement, marked atrophy, and adhesions of the apical lobe of the lung. (13561; 1/3×).

Case 5 (*Ovine*, 13561).

The subject was a sheep slaughtered at the Pretoria Abattoirs and from which a specimen was kindly collected by Dr. H. H. Curson, of this Institute.

Macroscopically, the specimen (Fig. 98) consists of the right lung, attached to the mediastinal surface of the lower part of whose apical lobe is a massive greyish-white tumour measuring 18 cm. antero-posteriorly, 11 cm. dorso-ventrally, and 9 cm. transversely.

This tumour is oval or bean-shaped with a depression in the middle of its dorsal border at the point where the lung becomes adherent. From here, the apical lobe, which is thinned to a paper-like membrane, stretches downwards as a broad band across the middle of the lateral surface of the tumour, whose ventral border it does not reach. The pulmonary pleura is closely attached to the tumour by several radiating bands of connective tissue, but there is no evidence of invasion of the pulmonary tissue, the tumour being in general smooth, covered by glistening serosa which is actually the pleura of the expanded cranial mediastinum (as is clearly seen ventrally, where a portion of the latter, excised with the tumour, is seen to be reflected over the tumour to provide its serous covering). On the left surface of the tumour also, a portion of adherent, compressed pulmonary tissue is present, obviously corresponding with the apical lobe of the left lung. In places the tumour bulges grossly beneath its serous covering, and also forms small irregularly outlined protruberances ca. ·5 cm. in diameter, limited by the serosa only. Elsewhere a definite capsule, 2 mm. in thickness, underlies the serosa. This capsule is tensely distended by the neoplasm. The lung, apart from displacement and pressure atrophy in the neighbourhood of the tumour, shows no changes.

Microscopically (Fig. 99) the tumour is enclosed by a loose-textured connective-tissue capsule, whose outer surface is covered by (pleural) mesothelium and which does not sharply circumscribe the tumour parenchyma which extends as prolongations through the capsule to within a short distance of the serosa. The tumour has a much branched and irregular stroma, consisting of a very loose connective tissue containing many fibroblasts and but sparse collagen fibres. This provides an extremely indistinct demarcation of parenchymal lobules, into which extend irregular intralobular prolongations of the stroma. Thus the stroma is, while quite prominent, poorly collagenised and irregularly formed, so that at best an indistinct lobulation obtains; the parenchymal cells appear to infiltrate the stroma just as they do the capsular investment and only on high magnification is the demarcation of stroma and parenchyma at all clear. The stroma is rich in thin-walled blood-vessels.

The parenchyma is immediately reminiscent of thymic tissue. There is no demarcation of lobules into cortex and medulla, but the structure is (as in the case of the thymus), that of framework of pale, vaguely outlined but apparently branching cells; having pale, vesicular nuclei, which supports and is largely obscured by the more numerous and darkly staining small round cells having the morphology of lymphocytes (thymocytes).

What appear to be condensations of the reticulum-like cells (for their elements have a similar morphology and continuity is easily traced) occur in the form of irregularly rounded agglomerations of epithelioid elements which are closely packed together, have indistinct outlines and a distinct tendency to concentric arrangement (Fig. 99). Typically the outer cells of these condensations, elongated and gently curved and having somewhat elongated nuclei, are arranged in two or more whorls which surround and are in continuity with the more centrally placed cells. The latter have a

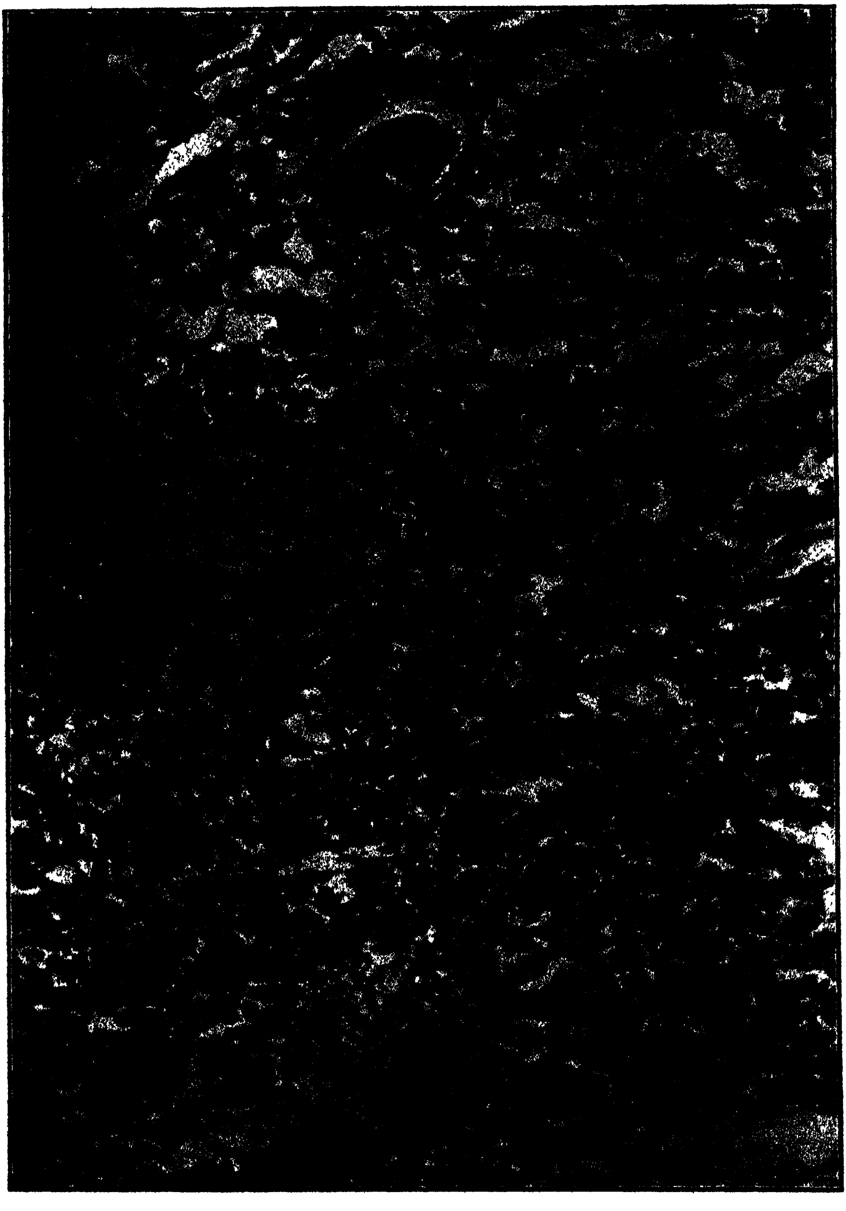

FIG. 99.—Structure of the thymoma of the sheep (fig. 92): Large, pale (reticulum) cells and variable numbers of small, round cells; above and below, formation of Hassall's corpuscles. (13561; 420×).

similar appearance except that they are more oval and have plumper and shorter nuclei. Similar condensations of cells may occur also in the form of elongated, narrow cords having a tendency to infiltrate the interlobular septa. These cell condensations remind one in all essential respects of developing Hassall's corpuscles and, furthermore, in not a few of them the central cells have undergone degenerative changes, viz. cornification, with thickening of the nuclear membrane, nuclear shrinkage, etc., in the manner familiar in the case of the fully developed concentric corpuscle of the thymus. Sometimes the small round cells may be present in among the epithelial condensations, which they give the appearance of infiltrating; but no distinct evidence of transition from reticulum-cell type to thymocyte type was obtained.

Both types of cell infiltrate the connective-tissue septa, but appear to respect the walls of blood-vessels, however thin these may be. Scattered eosinophile granulocytic elements are to be seen in both stroma and parenchyma; some appear as mature granulocytes, others to be in the myelocytic stage.

Sections through the attached area of the lung show a localised, chronic, productive pneumonia, without tumour invasion.

No nucleolar enlargement was observed. The M.I. is roughly 3.

Remarks.—The position of this tumour—in the precardiac mediastinum—its topography, the features of encapsulation with capsular and stromal infiltration, and above all the histology, viz. a framework of reticulum-cells (unassociated with a fibrillar reticulum) which supports cells of the thymocyte type and which cells undergo concentric condensations, wherein the elements assume definitely epithelioid appearance and show a tendency to degenerate into bodies resembling concentric corpuscles, stamps this neoplasm as a thymoma. No fuller criteria of its nature could, indeed, be desired. This was the only thymoma in which mitoses were at all frequent. The count mentioned has not been included in the table on page 31.

Case 6 (*Ovine*, 2536).

No details of the subject are available. The specimen consists of portions only of a neoplasm covered by a roughened serous membrane (pleura) and having a soft consistence like lymphoid tissue. To parts are adherent pieces of lung which have been ablated together with the tumour. Microscopically, the tumour tissue is seen to be strongly encapsulated by the thickened subpleural tissue and although there are signs of invasion of this capsule there is no encroachment on the pulmonary tissue. There is a moderately prominent connective-tissue stroma which very incompletely separates lobules of parenchyma. The latter is composed of two types of cells. Small round cells predominate in most places and are supported in the meshes of a syncytium constituted by stellate or spindle-shaped elements which are palely stained. Here and there the latter form condensations in which the elements are now of distinctly epithelial appearance, and occasionally there is a tendency to a concentric arrangement of the cells accompanied by increased acidophilia of their cytoplasm (Hassall's corpuscles). Eosinophiles are present but very sparse. The M.I. is 0.

Diagnosis.—Thymoma.

Case 7 (*Caprine*, 12797).

The subject was an adult ("full mouth") Angora she-goat which came to autopsy at this Institute. It was stated to have been in "very good" condition and was, in fact, inclined to adiposity. At post-mortem a bulky tumour was found to occupy the precardiac and also a part of the cardiac mediastina, reaching from the thoracic inlet to a point ventral to the bifurcation of the trachea. It was cream coloured, of soft and very friable consistence, and appeared largely necrotic, containing many amorphous, chalky centres. The specimen measures roughly 25 cm. long, 15 cm. dorso-ventrally and 11 cm. in width. It is irregularly lobed and of indefinite shape, adapting itself to the cranial portion of the thoracic cavity and the organs contained therein. In part it is covered by the mediastinal pleura but it often protrudes through the latter in the form of naked bosselations. The pericardium, especially on the left side, is closely surrounded but not invaded, the tumour here lying beneath the pericardiac pleura. Many detached masses, nodular or plaque-like in form, are found on the mediastinal and left apical pulmonary pleurae. They vary from 2 mm. to 5 cm. in diameter and the irregularly rounded nodules may be distinctly pedunculated, being attached by strands of newly-formed fibrous tissue. The apical lobe of the left lung is displaced dorsally and is much thinned (1 to 2 mm.). The nodules are confined to its pleura and do not invade the underlying pulmonary tissue. There are no metastases either in the bronchial or mediastinal lymph-nodes. Other interesting autopsy findings were a greatly enlarged thyroid (20 Gm.) and the presence of a (relatively) equally enlarged thyroid in the three-month foetus. The rest of the findings (chronic cholecystitis, acute catarrhal enteritis, *tumor splenis*, hepatic degeneration, hydroperitoneum, and hydropericardium) are scarcely relevant to our purpose.

Microscopically, sections from different regions of the tumour show that its greater part is in a state of total necrosis; outlines of the connective-tissue stroma enclosing caseous and often granular calcified material are all that is seen. Where the tumour tissue survives the structure is as follows:—There is a pronounced lobular structure due to a fairly uniform and well collagenised system of branching and anastomising trabeculae, which carry a moderate number of blood-vessels, in which wide lymphatics are often prominent and whose final ramifications, often some 15μ in thickness, completely, but more usually incompletely, separate the units of the parenchyma. These lobules vary in size, but are often about ·5 mm. in diameter and are rounded, oval, or polygonal in outline. They are constituted by two types of cell, which vary much in their relative numbers in different parts:—

(*a*) The first is a branching cell in apparent continuity with its neighbours. It has a poorly defined, but extensive, faintly eosinophilic cytoplasm and a large, oval or irregularly oval, extremely amblychromatic nucleus, usually between 8μ and 12μ in long diameter. These nuclei show poorly developed nuclear membranes and a very inconspicuous and delicate chromatin network. Nucleoli, when visible (which is not the case in the majority of nuclei), are inconspicuous and do not exceed, in n : N ratio, 1 : 50. These cells, anastomosing by means of their stellate cytoplasmic processes (i) form a reticulum in which the second type of cell is supported, often being present in such numbers as almost or completely to obscure the large, pale cells; or (ii) in some parts, where the second type of cell is absent or in smaller numbers, may form more solid sheets in which the cell morphology may better be studied. In these latter areas two morphological modifications of the supporting cells may be seen: (*a*) the cells sometimes show the faintest tendency to arrange themselves around a central, extremely indefinite " lumen " some 30μ in diameter, which is largely occupied by the rarefied cytoplasm of centrally-lying cells of the same type. This tendency is not at all striking and is only observed on close scrutiny; (β) occasional condensations of these cells form bodies resembling the concentric corpuscles of Hassall but somewhat more irregularly formed and of far less constant occurrence. The cells arrange themselves in irregularly concentric fashion about a central mass of degenerate elements which have a strongly eosinophilic cytoplasm of hornified (hyaline and lamellated) appearance and fragmented nuclei. The surrounding cells (from without inwards) develop fine granulations and then a definite eosinophilia of their cytoplasm and their nuclei become somewhat larger and hyperchromatic (thickened nuclear membrane and a few scattered chromatin granules, the nucleus, however, still remaining decidedly vesicular in type). These corpuscles may reach a (longest) diameter of 120μ, more usually they measure less than 75μ.

(*b*) The second type of cell resembles in all respects the small lymphocyte (or the " thymocyte ") and its morphology need not be further described. These cells are present in most variable numbers, often entirely obscuring the pale " reticulum " cells of an entire lobule; at other times they are concentrated in small (but ill-defined) foci in parts of the lobule. Sometimes these foci are situated for preference towards the periphery of the lobule, so that the resemblance to a lobule of the thymus gland may be increased by the fact that the central (medullary) portion is comparatively free from the small cells. Further it is in this central portion that the concentric corpuscles are situated (as in the normal thymus). In parts the small round cells may be almost or entirely absent from a lobule or a portion thereof and here the more solid structure of the reticular cells is seen. But whatever their arrangement, the variations in the distribution of these small round elements is responsible for a variegated light and dark staining, as seen in thymic tissue, but without the regular (medullary-cortical) pattern of the latter.

I cannot say whether transitions occur between the two cell types. The appearances are not inconsistent with such a view, but one is of course familiar with the difficulties of making such statements when dealing with lymphoid-like tissue. Strands of tissue containing both types of cells may be seen invading the stroma and pushing apart the collagenous tissue along its natural cleavage lines, and not infrequently this invading tissue grows into immediate contact with and bulges inwards the intima of thin-walled vessels of venous and also apparently of lymphatic nature. The actual act of penetration was not observed in the sections studied but in several cases the lymphatics contained loose masses of lymphocyte-like elements which, since among them occur cells of the reticular type and even of the type entering into the formation of the concentric corpuscles, are undoubtedly derived from the neoplasm, showing that such intravascular invasion had indeed occurred. The small lymphocyte-like cells may also arrange themselves to cover, in a single layer, the surface of loose masses of fibrin within the vessels. Sparse eosinophiles are to be seen infiltrating the stroma and also occurring in the parenchyma. The great majority of them appeared clearly of adult type (leucocytes). Mitoses are absent.

Both foetal and maternal thyroid show a pronounced goitre of parenchymatous type.

Remarks.—A largely necrotic, bulky, but slowly growing tumour of the cranial mediastinum, partially encapsulated by the pleura and often also penetrating the latter. It forms multiple secondaries on both parietal and visceral pleurae, apparently mainly by transcoelomic implantation, but very probably also by lymphatic metastasis in the subpleural plexus. Histologically it shows a tendency to invade its stroma and to penetrate vessels. It has a lobular structure and duality of parenchymal elements as well as concentric corpuscles clearly reminiscent of thymic tissue. Cysts lined by epithelial-like elements are scarcely formed, there being only a vague tendency to such. In the same subject were found pronounced parenchymatous goitre and a similar affection of the foetus.

Diagnosis.—Thymoma.

SUMMARY.

The apparent rarity of thymoma and the meagre records of this tumour among domestic animals prompted a closer investigation of the features on which this diagnosis may be based. There are reported, in addition to cases in bovines (in which the disease is already recorded), 2 cases in sheep and a case in an Angora goat, species in which thymoma has not to my knowledge previously been observed. The fact that some of these tumours had erroneously been diagnosed as lymphosarcomas or "round-celled" sarcomas makes it probable that the tumours occur more frequently than the literature indicates but that they are not recognised as such. It is interesting that thymoma is the only malignant internal tumour that we have encountered in goats, all the other malignant neoplasms of this species being skin tumours (epitheliomata). Whether the fact that this case was encountered in an Angora goat, a breed which we know is especially liable to cutaneous neoplasms, indicates that the susceptibility of this breed to malignant tumours is not only confined to cutaneous neoplasms cannot be decided on the basis of a single case, but is worth bearing in mind.

In ruminants, tumours of whitish colour and soft consistence lying in the precardiac and sometimes extending into the cardiac mediastinum or into the neck, displacing the apical lobes of the lungs dorsally and causing interference with the structures passing through the thoracic aperture should be suspected of being thymomas. The diagnosis is to be confirmed microscopically by the following features: duality of the cell types constituting the parenchyma, viz. (1) pale staining, reticulum-like cells which declare their non-mesenchymal nature (*a*) by being not (or at least not clearly) associated with fibrillar reticulum, (*b*) by tending to form more solid sheets, (*c*) by often lining clearly cystic cavities and assuming an epithelial morphology, or in other cases showing at least a faint tendency in this direction, (*d*) by usually forming (5 cases out of 7) bodies strongly resembling the concentric corpuscles of the thymus, and (*e*) by sometimes forming concentric whorls which do not degenerate into Hassall's corpuscles; (2) small round cells having the morphology of "thymocytes" (lymphocytes) which are supported in variable numbers by the reticulum-cells and whose distribution causes often an alternation of lightly and darkly staining areas as seen in thymic tissue. The conception of the passive behaviour (secondary nature?) of these cells is questionable in view of their ability in one case to penetrate vessels and their frequent tendency, along with the large pale cells, to invade the stroma. Eosinophils were found almost constantly to be present, often differentiating locally from precursors in the myelocyte stage. The tumours are encapsulated by the mediastinal pleura, but tend to invade this capsule and also their stroma; so that, in spite of their slow growth (mitotic index nil or very low), they are to be regarded as malignant and in their ultimate development are responsible for serious and fatal results. They are not, in most cases, associated with nucleolar enlargement, thus forming yet another possible exception to the generalisations of MacCarty and Hammeder, regarding the constancy with which this change accompanies the malignant process; yet it must be admitted that only a low grade malignancy is present. The lobular structure of the tissue, resembling normal thymus, may be pronounced, but is variable in development. The most important differential diagnoses are endothelioma (on account of the cell characters and especially the whorled arrangement sometimes found), mesothelioma (which we have not found affecting the pleura in our material but which no doubt might be distinguished on the basis of the microscopic morphology—see Chapter VI), lymphocytic tumours ("round-celled" sarcoma, lymphosarcoma)—to be discriminated on the basis of evidence of the epithelial, not mesenchymal, nature of the reticulum cells, and lastly the canine heart-base tumours (Chapter XI), whose location is, however, apparently specific and whose cytology is totally different.

CHAPTER VI.

Mesothelioma.

DEFINITION AND TERMINOLOGY.

By mesothelioma is understood a tumour which arises from the lining cells of the coelom, whether of its pleural, pericardiac, or peritoneal sub-divisions. Although much criticism has been levelled at the use of this term (originally introduced to denote tumours having their inception in the elements of the adrenal cortex, but by nearly all authors long ago abandoned in that sense) it is coming increasingly into favour and is now in very general use. The objections to its use appear to arise from two chief sources:—(*a*) There are those who, ignorant or unappreciative of those complications of embryological and histogenetic theory on which any sound classification of coelomic tumours must be based, see in the introduction of such a term merely a needless complication of an already difficult tumour nomenclature. (*b*) A group of objectors more worthy of attention are those who, having made a close and critical study of the above difficult considerations, have arrived at conclusions which they regard as sufficiently definite to allow of the identification of the tumours concerned with already existing groups of neoplasms.

The whole subject has within recent years been most competently reviewed by Grossek (1932), dealing with the human subject, and it is not necessary for us to do more here than to outline in brief the main considerations on which the controversy is based. This at least it is advisable to do, since in the veterinary literature no competent discussion of the subject occurs, most authors apparently being content to follow the classification adopted by any human pathological work which happens to be conveniently to hand.

It must at the outset be understood that the difficulty of classifying growths arising in serosae is threefold:—Firstly the common occurrence of secondary neoplastic lesions of serosae (which may arise by true metastasis, or by continuity growth, or most often by transcoelomic implantation) in man has led to some uncertainty in deciding whether given serosal lesions are of primary or secondary nature. As Willis (1934) remarks with justification: " The diagnosis of primary tumours of serous membranes has frequently been made on wholly inadequate grounds and with insufficient appreciation of the frequency with which small primary carcinomatous growths may yield massive widespread coelomic deposits ". He goes further than we are willing to follow him, however, when (like Robertson, 1923 and 1924) he doubts the occurrence of any cases of primary tumours arising from serosal cells. Yet a number of authorities have believed in the existence of such tumours, notably Ewing (1928), Mallory

(1923) and Aschoff (1923), in their textbooks, and the occurrence of primary coelome tumours (other than those of the "connective-tissue" group) has found very general acceptance among teachers of pathology.

Secondly, providing that the occurrence of primary coelome tumours be admitted (apart from those of the "connective-tissue" group), a difficulty arises in distinguishing between those that may arise from the coelomic lining cells and those that may have their origin from the endothelial lining cells of the subserous lymphatics. Among authors admitting the existence of the tumours in question there have been those who have denied the one group and those that have denied the other, while many are willing to admit both kinds, which should then, as pointed out by Grossek, be clearly distinguished nomenclaturally. The problem is not made any the easier by the possible origin of tumours from misplaced epithelial nests in the serosa.

Lastly, assuming that we are in a position to separate tumours arising from the covering cells of serous membranes from such as may originate from lymphatic endothelium, the difficulty arises as to how these neoplasms are to be designated terminologically. It would be beyond the scope of this work to enter into a detailed discussion of the controversy surrounding the nature of the coelome lining cells. Every elementary student of histology is aware that little help is to be obtained in this connection from the standard textbooks of histology and gathers readily from his reading of such that as many authors term the cells in question "endothelial" as "epithelial". It may be briefly recalled here that this lack of uniformity centres round a controversy of triple nature and which concerns (*a*) the embryological derivation of the cells, (*b*) their morphology, and (*c*) their biological reactions:—(*a*) Those who (following the coelome theory of the brothers Hertwig) derive the coelomic lining from ectoderm, would have it that the cells are epithelial, while those who see in the lining cells merely a specialisation of mensenchyme (dependent on environmental relation to a cavity) would term them endothelial. (*b*) It is to be admitted that the precise definition of epithelial cells is somewhat vague; and that, notwithstanding the close morphological similarity of coelome lining cells to vascular endothelium, there is yet on purely morphological grounds no fatal objection to terming the cells in question epithelium. This procedure gains considerable support from the fact that (at least in some species), at certain sites or in certain stages of development, the cells in question are ciliated(¹), a phenomenon which is decidedly foreign to our conception of the endothelium. (*c*) The biological reactions of the coelome cells in tissue culture and in normal and pathological transformation provide perhaps the most interesting of all evidence. The somewhat extensive literature in this connection provides evidence regarding (i) the ability to develop cilia as temporary structures, (ii) the faculty of forming connective-tissue fibrils, and (iii) the tendency, in proliferation, to assume

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(¹) Cilia have been observed by v. Brum (in the pleura of the dog), by Maximow (1927) in the omentum and mesentery of rabbits, and by me in the horse ("germinal epithelium" of the mare) and under pathological conditions in the domestic fowl (unpublished data) as well as in coelome tumours.

columnar form and to enclose lumina. Authorities have variously assessed this evidence as providing justification for the view that the cells in question are intermediate between the connective-tissue type and the epithelial type (Maximow, 1927) or that they are predominantly or exclusively epithelial in nature (Grossek).

In view of the highly controversial nature of the evidence, it appears desirable at the present time to take a middle course and designate the cells as mesothelial, a term which already enjoys considerable acceptance. As a corollary of this, it follows that we cannot do otherwise than name the tumours arising therefrom as " mesotheliomas ". The two alternative terms, carcinoma and endothelioma (of pleura, peritoneum, or pericardium, as the case may be), commit one definitely to a decision on the controversy regarding the epithelial or endothelial nature of the cells, while the latter term has the additional disadvantage of providing no means of distinguishing, among serosal " endotheliomas ", those that arise from the surface cells and those derived from the subserous lymphatics.

OCCURRENCE.

In man one gathers from the literature that mesotheliomas are rare tumours, the existence of which is denied by several authors. Grossek, in his review, collects 30 cases and adds one of his own. In animals, mesotheliomas have not seldom been mentioned. Feldman (1932)) found one among 43 equine and two amoung 230 bovine tumours, and he remarks that " they must occur more frequently in lower animals than is indicated by reported cases ". Of the reports in the veterinary literature, all of which are collected by Feldman in his textbook, and numbering 5, scarcely any are provided with a detailed histopathological description and although there may be no grave reason to doubt the nature of any of them(²), one could desire more accurate information. The case reports concern 2 horses and 3 cattle, apart from those of wild animals reported by Scott (1927). In horses affection of the pleura and in cattle, of the pleura (in two cases of Feldman's) and peritoneum (one case of Purman) are mentioned.

The Onderstepoort collection contains no fewer than 3 certain cases of mesothelioma (two in bovines and one in the horse). From my own experience and from the information in the literature there is no record of any other domesticated species being affected by these growths(³).

PATHOLOGY.

In describing the cases encountered in South Africa, we shall consider the tumours in the following groups: those arising from the peritoneal, pericardial, and pleural mesothelium respectively. Of the latter the collection contains no well authenticated case, but under that heading it will be convenient to mention a tumour of the horse that by some might possibly be regarded as a primary mesothelioma of the pleura.

(²) The suspicion that some of Feldman's cases were thymomas has already been expressed.

(³) Feldman pictures, but does not describe a case of " mesothelioma of the visceral pleura of a sheep ".

1. *Peritoneal Mesothelioma.*

Case 1 (*Bovine*, 12147).

The specimen (Fig. 100) consists of a portion of omentum of a bovine (age and sex not known) kindly sent in by Dr. G. Martinaglia from the Johannesburg Abattoir. Its surface is covered by multiple flattened nodules which vary in diameter from *ca.* 1 mm. to 1 cm., but more often are confluent to form large irregular plaques having an uneven surface. Adjacent nodules are often connected by fibrous filaments. A peculiar striped appearance of the membrane results from the exposure of the omental fat in streaks alternating with the neoplastic tissue. In some parts the newly formed tissue affects only one surface of the membrane, but in the case of the (older) more extensive plaques the whole thickness of the serosa is occupied, the tumour appearing on both surfaces. The consistence is rather tough and a rich system of connective tissue is visible on section throughout the softer substance of the tumours. The colour is not preserved.

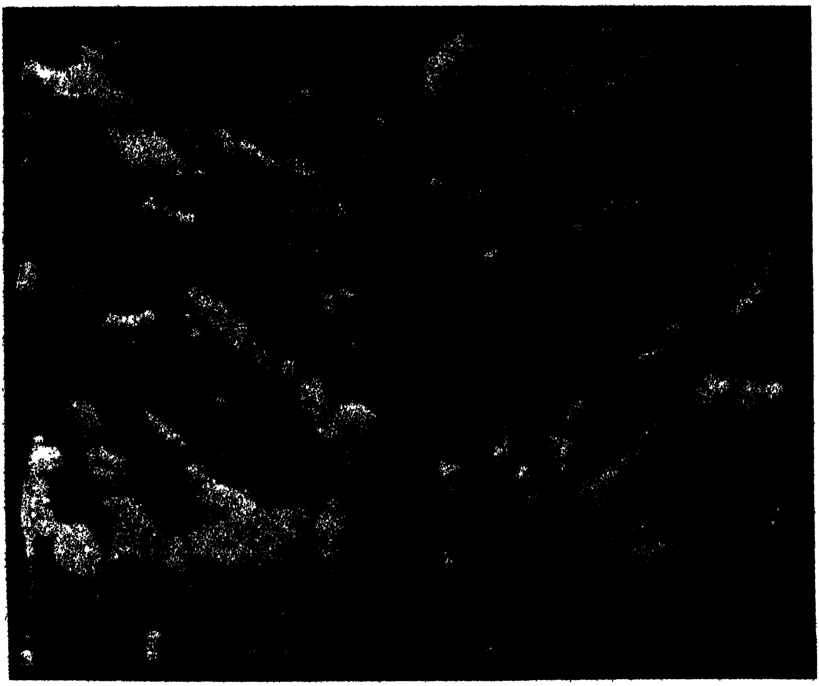

FIG. 100.—Gross appearance of omental mesothelioma of the ox: Flattened plaques of neoplastic tissue between which the omental fat is visible (12147; 3/4×).

Microscopically (Figs. 101 and 102), the neoplastic parenchyma is seen to grow exclusively in pre-formed spaces in the fibrosed omentum, in many of which an endothelial lining is still present; in other words it grows intralymphatically and its " stroma " is thus largely pre-existent. The omentum shows a great increase of well-differentiated connective tissue and the tumour cells are largely

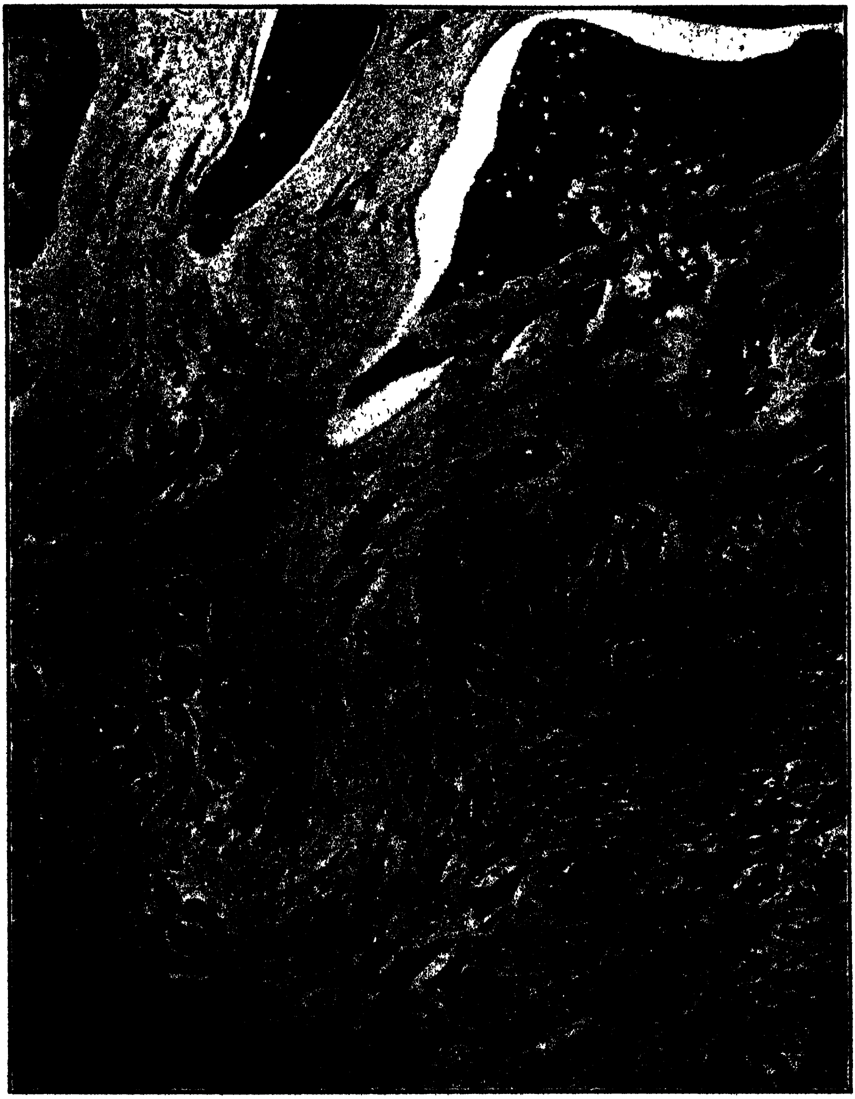

FIG. 101.—Mesothelioma of the omentum of the bovine (fig. 100): Intralymphatic growth in larger (above) and smaller (below) vessels of the subserosa; note the small lumina which are formed. (12147; 60×).

arranged (following the course of the lymphatics) in elongated, narrow cords (one or two cells in thickness), which branch and which, here and there, become continuous with more massive and (in transection) rounded tracts of cells around which the walls of the lymphatics have been expanded. A somewhat scirrhous appearance thus results and is a striking feature of the microscopic picture. The cell cords and masses are, at least in respect of one-half of their circumference, retracted from the enclosing walls, so that a narrow peripheral space is seen. This feature is possibly a fixation artefact, but appears more likely to depend upon the pressure of the lymph-flow along that aspect of each tumour cell-cord at which the nutrient vessels do not enter—see Fig. 101 (right top corner).

The cells are, for the most part, polyhedral elements of moderate but variable size (7 to 20μ in diameter) and are usually distinctly outlined on account of the presence between their apposed borders, of narrow clefts (possibly a fixation artefact). Those at the periphery of the groups or cords have a distinct tendency to assume an irregularly columnar form, standing vertically to the long axis of the (vascular) space occupied by the cell mass, i.e. radiating from the circumference towards the centre of what was previously the vascular lumen. Often the proximal ends of such cells are expanded, giving a "tailed" appearance to the cells. Their nuclei are usually of short-oval shape and are characterised by a sharply defined membrane and a close-meshed, fine and delicate chromatin network. A single central nucleolus, which stains intensely, is a prominent feature, contrasting sharply with the amblychromatic nucleus. The nuclei average some 4·5 to 6μ in diameter, but much larger nuclei may be encountered in less typical cells. The n : N ratio is usually between 1 : 14 and 1 : 9.

Between the peripheral cells of the cords and the stroma (i.e. the lymph-vessel wall) and retracted from the latter together with the cells, to the bases of which it is closely adherent, is a prominent band (i.e. a cylinder) often measuring 5μ in thickness, of hyaline substance (yellow with picric acid, extremely pale mauve with haemalum-eosin, blue with Mallory's triple stain) standing in the relation of a basement membrane to the peripheral cells. A similar substance may occupy rounded lumina which often occur in the central portions of the larger cell masses. In these hyalinised spaces, cell-debris and sometimes degenerating cells are also to be seen, the former often appearing as delicate fibril-like strands. These spaces, which are somewhat irregular in outline, are obviously produced by hyaline degeneration of the cells; they do not appear to be true lumina. The changes described confer on the neoplastic tissue the appearance familiarly known as cylindromatous, and in this respect the picture seen in practically identical with that illustrated by Borst (1, *Tafel* D, Fig. XLV) from a tumour diagnosed as "*hyalines Endotheliom (Cylindrom) der Orbita*".

The application of Mallory's triple stain shows that, at least in the majority of the alveoli, no intercellular reticular stroma is present. In some groups of cells somewhat indefinite results were obtained and it seemed possible that in some of the cells *intracellular* fibrils were present, but I cannot speak with certainty on this point as the picture provided by this (old, formalin-fixed) material is not so clear as could be desired. As mentioned above, it is further complicated by the fact that the " hyaline " substance takes a weak stain with analine blue. The mitotic index is 2.

Among the narrower cords a spindle-shaped tendency of the cells is sometimes seen. It is difficult to say whether this is merely the mechanical result of the accommodation of the cells within a narrow space or whether it represents a true growth-tendency.

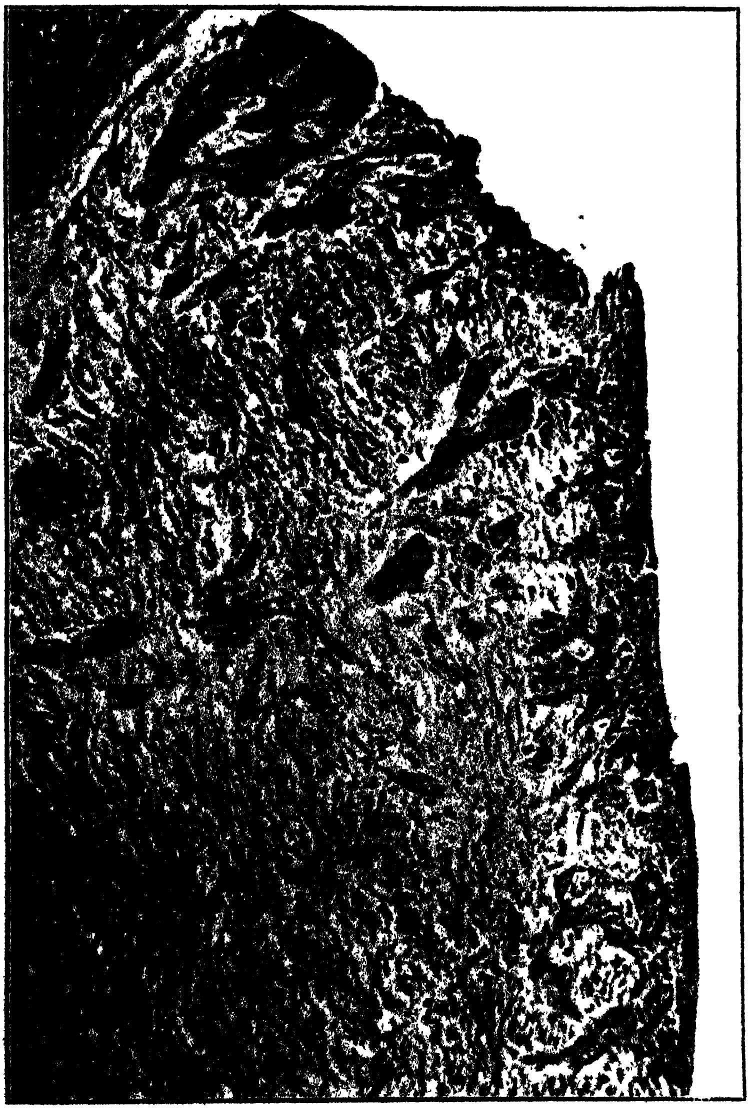

Fig. 102.—Surface of a small omental mesothelioma of the bovine (same case as fig. 101), showing continuity between downward-proliferating mesothelial cells and the intralymphatically-growing tumour cells. (12147; 240×).

An open mind was kept regarding the origin of this tumour and the correct name by which to designate it until in certain of the sections the following appearances seemed to place the histogenesis beyond doubt. In the nodules in question (Fig. 102) there is an overlying covering of mesothelial cells; this mesothelium in places becomes thickened to form a layer several cells in depth, and from here branching and tapering strands proceed inwards through the subserous lymphatic plexus to become continuous with the groups of frankly neoplastic cells. The picture seen leads one irresistibly to the conclusion that a direct origin of the neoplastic cells from proliferating mesothelials has been demonstrated.

Remarks.—This is a primary tumour arising from the coelomic lining cells and growing almost exclusively by lymphatic permeation of the omentum. It occurs as multiple nodules and plaques and this multiplicity is seen to be, at least in part, of primary nature, since little difficulty was experienced in individual nodules in tracing a direct origin from proliferating mesothelium. That some of the nodules may have arisen by implantation is very possible, others of course arising by direct intralymphatic spread. The present case is important in that it serves to emphasize that in the case of tumours of the serosae an intralymphatic growth speaks by no means in favour of an origin from lymphatic endothelium (endothelioma), nor necessarily in favour of metastatic carcinoma. Both these diagnoses were fully considered and especially the latter which, in the absence of the assurance that a competent and exhaustive search at autopsy had revealed no primary tumour elsewhere, could not have been excluded (*a*) unless there could be shown to be morphological peculiarities of mesothelioma which alone may serve for its recognition, a circumstance which appeared to me to represent the truth only after further cases had been examined, or (*b*) unless direct evidence of primary origin, as obtained in this case, could be shown.

Diagnosis.—Mesothelioma of the omentum.

Case 2 (*Bovine*, 6458).

The museum specimen (Fig. 103) consists of a large portion of bovine omentum affected by lesions very similar to those described in the previous case. There are smaller discrete nodules, but more especially there are extensive flattened plaques reaching a diameter of 8 cm., very slightly raised above the surrounding surface, and sometimes penetrating the whole thickness of the omentum to appear on both surfaces. Adjacent plaques are often connected by fibrous filaments. Small islands of omental fat may be exposed in the centres of these larger plaques. The surfaces of these plaques lack the glistening appearance of frankly subserous tumours; they appear duller, without a " hard " sheen.

Microscopically, alveoli and strands of cells without intercellular stroma are seen to lie dispersed to a variable degree in a rich collagenous stroma. They appear largely or exclusively to occupy preformed spaces, from the walls of which they have often shrunk away and to which remnants of an endothelial lining can often still be demonstrated (intralymphatic growth). These spaces with their contained cell-masses are especially closely aggregated towards the surface of the lesions, while more deeply they are widely scattered as narrower bands in a massive connective-tissue stroma (scirrhous appearance).

The cells are clearly identical with those previously described in Case 1. They are polyhedral elements which often show a tendency to columnarity, resting vertically against the enclosing connective tissue; or they may tend to be spindle-shaped and somewhat flattened against the stroma. There is often rarefaction in the centres of the alveoli so that ill-defined spaces arise, but one could scarcely speak of lumen formation. The individual elements commonly measure some 10 to 12μ in diameter. Their cytoplasm is not very distinctly outlined and is somewhat poorly stained, not dense, and basophilic. It appears more condensed in (degenerating) elements with pycnotic nuclei. The nuclei are fairly uniform in appearance, usually of short-oval shape, 7·5 to 9μ in diameter, occasionally showing minor irregularities (slight angularities, serrations, etc.). The nuclear membrane is sharp and distinct and encloses a very pale nucleoplasm characterised by a fine and even network of chromatin. The nucleoli, which are as often double as single (less often 3 or 4 are visible), are usually central or moderately eccentric (rarely markedly eccentric). They are prominent, both on account of their size and because their deep staining contrasts strongly with the nuclear amblychromasia. They are often discrete and rounded and deeply stained, but many are somewhat indistinctly outlined.

FIG. 103.—Gross appearance of another mesothelioma of the omentum in the ox: Flattened plaques of neoplastic tissue between which the omental fat is visible. (6458; 1/2×).

oval, or dumb-bell-shaped (apparently fusion of two nucleoli) and some show a tendency to a lighter staining (vacuolation?) although no definite inclusion-body-like transformations are seen. The n : N ratio varies from 1 : 14 to 1 : 25. The cells and their arrangement are somewhat reminiscent of the elements of the adrenal cortex.

Small, calcified, and concentrically striated bodies are prominent features among the cell groups. They vary from the size of a cell to larger agglomerations reaching a diameter of 60μ. They can usually be seen to contain centrally a degenerated tumour cell. They are clearly of the general class of degenerative bodies usually but unsuitably called *corpora amylacea* and their origin is to be ascribed to concentric deposition of calcium salts around a nucleus provided by a degenerate tumour cell.

The mitotic index is 2.

The histogenesis of the nodules available for examination could not be traced to the mesothelium and in the diagnosis one has to rely on the close morphological resemblance (both macroscopically and microscopically) to Case 1, disregarding the non-essential features such as degenerative calcific changes.

Diagnosis.—Mesothelioma of the omentum.

Summary of the Pathology of Mesothelioma in Bovines.

The preceding study of bovine mesotheliomas shows that these tumours are among the less frequent neoplasms encountered in bovines in this country, but that they need not be regarded as great rarities. They were only found in connection with the peritoneum, pleural mesothelioma of the bovine not having been observed in this country(4). The lesions were confined to the omentum. Macroscopically they are characterised by a multiple appearance, which, as a microscopic study shows, must be considered—at least in part—as primary, although extensions of, secondary nature obviously also are favoured on account of intralymphatic spread. They appear as flattened lesions, usually forming extensive plaques, which often penetrate the whole thickness of the omentum. They have a duller or softer appearance and are less prominent than the lesions of secondary serosal carcinosis, which owing to their subserous situation have a " hard " sheeny appearance and which are often very firm and fibrous in consistence on account of the fibrosis which their growth evokes. Mesotheliomas lack the multilobulate appearance of most tumours of lymphangiogenous origin. Metastasis was not observed, except locally. The microscopic study shows that the origin of these growths from proliferating mesothelial cells may be traceable. As stated above, this traceability affords evidence of primary multiplicity. It appears that the normally flattened mesothelial cells become mobilised, an expression which we use to indicate that they assume a columnar to cuboidal form, may evoke a reaction in the connective tissue of the subserosa whereby the latter forms the propria for papilliform elevations, may become several layers in depth, and at an early stage penetrate the immediately underlying (subserous) lymphatics. From here extensive spread takes place largely or purely within the confines of the subserous lymphatic plexus. This growth is associated with a fibrosis of the (interlymphatic) subserosa. The lymphatics become filled out with the tumour cells, and on account of the surrounding fibrosis and the ultimate disappearance of the endothelium may afterwards become unrecognisable: a scirrhous appearance of the whole growth results. Within the preformed spaces, the tumour cell masses may remain unvascularised or may, later, especially when more massive aggregations are formed, become vascularised by means of a fine collagenous stroma.

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(4) Feldman mentions two cases of pleural mesothelioma of bovines in his collection, but from the microphotographs I at once suspect thymoma, a differential diagnosis which one does not feel certain that he considered.

The tumour cells, said by Ewing to have a characteristic morphology (which however is not actually described), are elements which usually have a polygonal shape, but also tend to assume a columnar form or to be flattened against the enclosing stroma. They vary considerably in size (from 7μ to 20μ) and are characterised by a delicate, basophilic homogenous cytoplasm. They were not observed to be associated with an intercellular reticulum. Their nuclei are fairly uniform, may lie centrally or eccentrically, usually fill about half of the cytoplasm, vary in shape from short-oval (the most typical) to long-oval, and often show slight angularities, depressions and serrations. They are highly characteristic, having a sharp but delicate nuclear membrane and an evenly-distributed, fine chromatin meshwork, being distinctly amblychromatic, and showing one or two (sometimes 4) deeply staining, prominent, central, slightly eccentric, or markedly eccentric nucleoli. In any one tumour the great majority of nuclei do not vary greatly in size, but in the different tumours they measured from 4·5μ to 12μ. The nucleoli are characterised by prominence, deep staining, and ratios which varied between 1 : 9 and 1 :25. The formation of "intranuclear inclusions" from nucleoli was not observed, and these or other extreme cellular atypicalities should therefore at once raise the suspicion that one is dealing with secondary carcinosis or with tumours of some other kind.

There is a considerable tendency to secondary changes, which may confuse the diagnosis. Necrosis may be prominent, as also necrobiotic changes whereby the cell cytoplasm becomes strongly acidophilic and the typical nuclear pattern disturbed by hyperchromasia and pycnosis. In one case extensive hyaline formation was seen, leading to a "cylindromatous" morphology, while in another case "corpora amylacea" almost dominated the picture.

In the differential diagnosis, macroscopically, a chronic tuberculous peritonitis (grapes) must be mentioned, although there is really little similarity in appearance to mesothelioma, the lesions being far more likely to be confused with secondary carcinoma. Further, secondary carcinomatosis of the serosae (Figs. 104, also 85 and 86) and primary endothelioma arising from lymphatic endothelium have to be considered. In bovines secondary serosal carcinomatosis is not very common in our experience; this is presumably to be ascribed partly to the fact that the only common internal (glandular) carcinoma in the country is liver carcinoma, which, when of the more usual hepatocellular variety, has little tendency to extrahepatic metastasis. Extensive serosal carcinosis may be seen secondary to cholangiocellular tumours and the description of such lesions (Chap. IV, Case 17) should be referred to in this connection. Bowel and gastric carcinoma, as well as ovarian carcinoma have not been observed in South Africa. (Acanthoma of the fore-stomachs is fairly frequent, and may also spread intralymphatically in the serosa, but the cells of acanthoma are of course easily recognisable). There is thus, especially when the very different appearance of secondary carcinosis is remembered, scarcely any danger of confusing carcinoma with mesothelioma, even where a complete autopsy has not been made. Further, we conclude that in any case the morphology of the tumours, especially the details of their

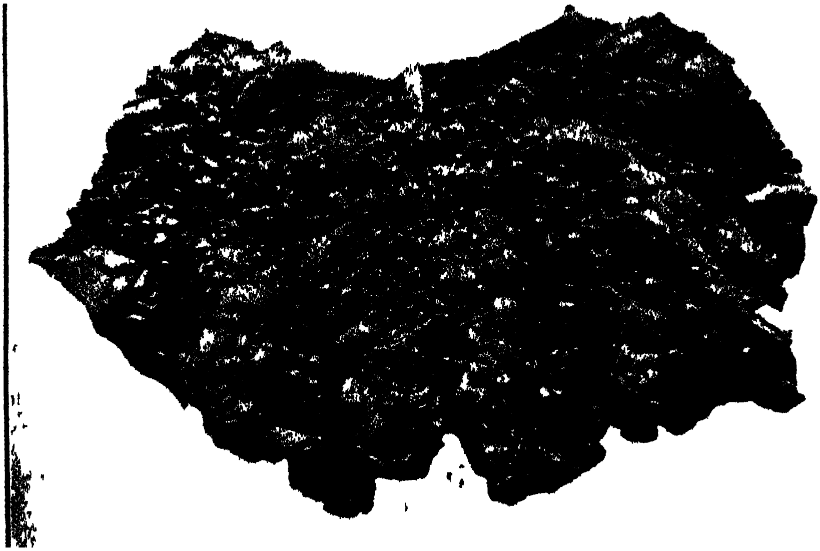

FIG. 104.—Secondary carcinosis of the mesentery of a mule; a lesion which macroscopically may be confused with multiple primary tumours. (2789; 1/2×.) See also figs. 85 and 86.

cytology, provide a characteristic picture which is specific for mesothelioma. Malignant or benign tumours of lymph-vascular endothelium are more likely to be confused, especially when appearing in multiple form. In bovines we have found that these assume a multilobular appearance instead of the single placques of mesothelioma; cyst-formation may be prominent; and the lesions again have a definitely subserous location, presenting a smooth and glistening surface. In human pathology it has been pointed out that there is a distinction between the growth-modes of mesothelioma and endothelioma, the former growing intralymphatically in the already existent lymphatics, as we have seen here to be the case, while the latter grows by vascular sprouting, i.e. formation of new tumourous lymphatic vessels. This is also a cardinal point in distinguishing these tumour types in animals. For the distinction of both secondary carcinoma and primary endothelioma, the observation of the direct origin from mobilising mesothelial cells, when it can be made, places the issue beyond doubt. The descriptions of lymphangioma and angiogenous endothelioma of serous membranes in Chapter VIII should be consulted in connection with the differential diagnosis from mesothelioma.

(2) *Pericardial Mesothelioma.*

This is probably one of the very rarest of neoplasms of domestic animals and in the literature I can trace only one well authenticated case, viz. that of Schlegel (1908) who reported such a tumour in a dog. Apparently these tumours are not known in other domesticated species, and in man also they are rarities (Monkeberg, 1924). Pericardial mesothelioma is on no account to be confused with mesothelioma of the pericardiac pleura: Feldman (1932) does not make this distinction clear when he mentions a case (without complete description, however) in which in a bovine a mesothelioma "involved the pericardium, the parietal pleura and the suprasternal lymphnode". It is obvious that those pleural mesotheliomas which happen to affect, *inter alia*, the pericardiac pleura will appear as "involving the pericardium".

Case 3 (*Equine*, 9663).

The subject was an aged black gelding which was destroyed in the preparation of horsesickness virus. Apart from the changes associated with that disease, verminous nodules in the liver, and the presence of accessory spleens, the only positive findings at autopsy were growths affecting the visceral (epicardium) and parietal layers of the pericardium. The largest measured *ca.* 3 cm. in diameter and was raised 1·5 cm. above the surrounding pericardium near its reflection on to the root of the aorta. Smaller nodules were described as being present on the epicardium in the neighbourhood of the coronary sulcus, on the right atrium at the apex of the heart and at other parts of the general heart surface. In the museum specimen, consisting only of the *aorta ascendens* and a portion of attached pericardium, the largest growth is seen to present a lobulated and somewhat irregular surface and to be ovoid in shape. Other nodules on the pericardium, some of which are confluent with this larger mass, vary in size from 1 cm. to 1 mm. The consistence is firm and glandlike and the colour (colour-preserved specimen) is a greyish-pink. With the naked eye, but more especially with the hand-lens, are seen minute (pin-point) cyst-like cavities on the cut surface. The surface of the smaller nodules is smoother, that of the larger ones roughened or irregular.

Microscopically (Figs. 105, 106), all stages in the development of the tumours, apparently as multiple primary growths, can be followed. (*a*) The earliest changes (Fig. 105) are not visible to the naked eye and have not (morphologically) as yet reached neoplastic grade: they consist merely of papilliform elevations (thickened by increase of collagenous tissue) of the propria of the pericardium, covered by mesothelial cells which may be somewhat plumper (less flattened) than normal, or may be cuboidal in shape. Here and there they show a tendency to be indistinctly ciliated. They are not more than one layer in thickness. Morphologically this is merely the lesion known in German as *Zottenherz*, a fibrous-papilliform hyperplasia of the pericardium such as occurs during organisation of an exudate. (*b*) In the smaller nodules (Fig. 106) there is a definite proliferation of the mesothelial cells, as follows: they vary from cuboidal to tall columnar, although some remain flattened, and usually quite distinct and unmistakable cilia appear. These cells cover the now very prominent papillae, on the sides of which small secondary papillae appear, the appearance being somewhat reminiscent of the *propria mucosae* of the vaginal portion of the oviduct of a fowl. The cells may, in parts, be more than one layer in depth, especially where they are still more or less flattened. Meanwhile,

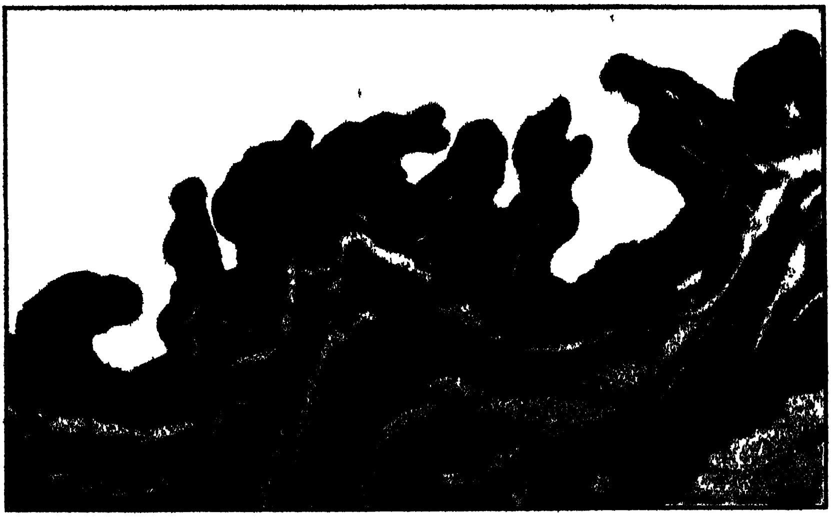

FIG. 105.—Early stage of proliferation of the pericardium of the horse which leads later to the formation of pericardial mesothelioma: Papilliform elevations of the serosa covered by mobilized and often ciliated mesothelial cells. (9663 ; 210×).

invasion of the propria occurs by cells of much the same appearance, but here arranged to line gland-like acini whose lumina may be considerably dilated (forming the small cysts seen macroscopically). The whole process nevertheless remains usually fairly superficial, although prominent thickenings are formed and a rich and well vascularised stroma derived from the propria supports the neoplastic gland-like structures. The lining cells of the acini are usually of the extremely tall columnar form and very narrow, but often also they are more cuboidal and occasionally even flattened. Cilia are often retained by these cells. The scanty contents of the acini consists of desquamated elements and tangled fibrillar structures which are the cast-off cilia (not fibrin: very pale blue with Mallory's triple stain). What I have spoken of as desquamated elements do not necessarily appear to have lost their vitality: they tend to become

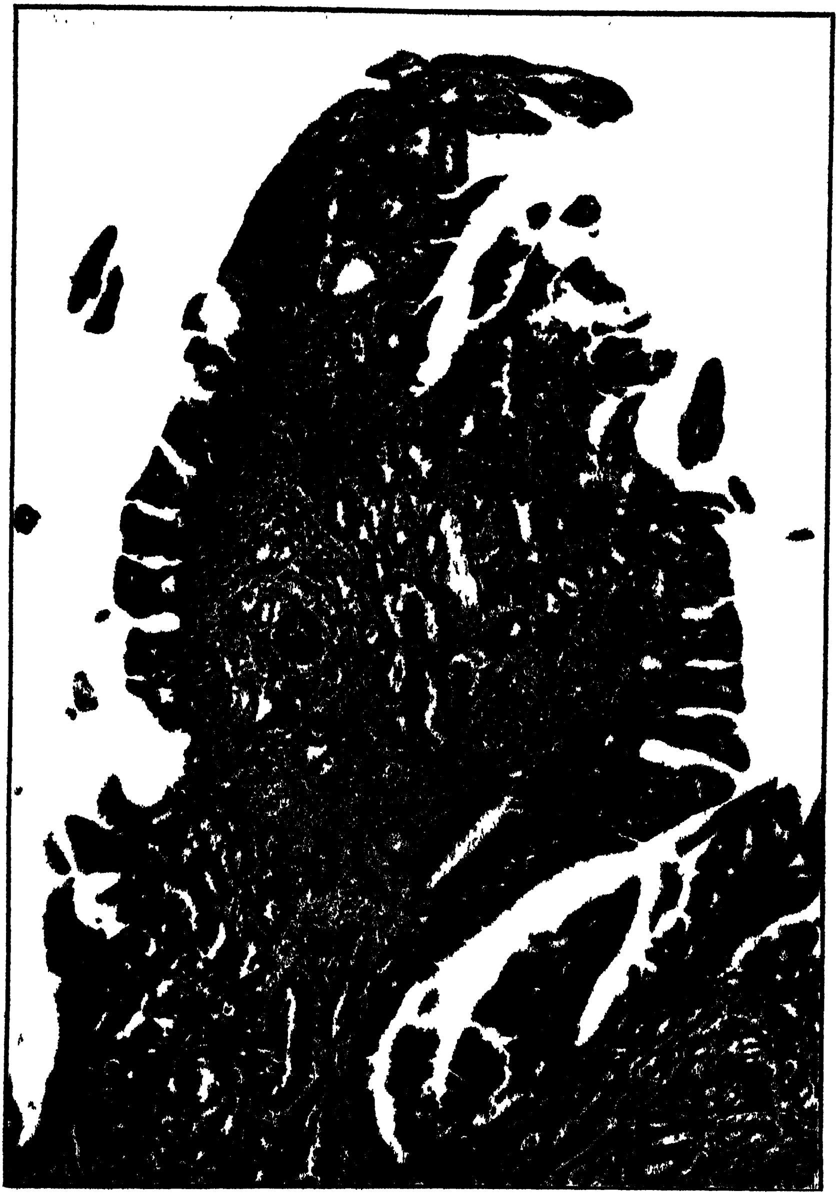

FIG. 106.—Later stage in the formation of pericardial mesothelioma in the horse (same case as fig. 105): Papilliform elevations with secondary papillae covered by columnar neoplastic mesothelial cells and commencing invasion of the subserosa by gland-like acini. (9663; 210×).

rounded up, sometimes while still retaining their cilia, and their cytoplasm stains more deeply (a dull reddish with haemalum-eosin). The same elements, no longer ciliated, often have their cytoplasm filled with coarse lipoid globules (macrophages, "foam cells"). (c) In the larger tumour the general appearances are similar. The extreme proliferation in the stroma of the acinar tissue has, however, resulted in a pressure atrophy (?) of a considerable amount of the overlying papilliform proliferations, which are often necrotic and apparently in process of being cast off to leave naked the deeper neoplastic tissue. The acini are less regular in size, the smallest being encircled by only three flattened cells, and measuring some 15μ in diameter; where such acini are present in numbers, which is especially the case in nodules taken from the epicardium, an appearance very similar to an angioma may result and the tumour here might easily be diagnosed (erroneously) as a capillary lymphangioplastic endothelioma. Sometimes the acini tend to lose their lumina and there are, in addition, thin, solid strands of cells which have lost polarity and are proliferating irregularly. Collagen and especially reticulum fibres often pass between these cells, and stroma and parenchyma consequently become confused; it is possible that the tumour cells themselves become fibroplastic, but this question was not decided definitely by the fibrillar stains applied.

The cells have amblychromatic, oval nuclei, a delicate nuclear membrane, and a very fine chromatin network. Larger nucleoli may be seen in the desquamated elements. In the very tall cells and also in the flattened ones the nuclei are of course elongated or spindle-shaped. Where the cells are closely crowded, the nuclei may be compressed to an angular shape.

Remarks.—The chief interest lies in the ciliation of the tumour cells and their transformation after desquamation into macrophage-like elements, both of which phenomena are well-known potentialities of the coelome lining cells. From the standpoint of practical microscopic diagnosis, the likelihood of confusion with lymphangioplastic endothelioma exists if an insufficient number of sections were to be studied.

Diagnosis.—Pericardial mesothelioma.

(3) *Pleural Mesothelioma.*

The Onderstepoort collection contains no certain example of this tumour and one could wish for more material before generalising on this subject. Feldman (1932) saw mesothelioma of the pleura in the horse, as did also Douville (1907). The following case also affected a horse, and while clinically there appears to have been a marked similarity to the two cases mentioned above, the tumour, at least in its cytology, differs markedly from the peritoneal mesotheliomas seen in bovines. It is here reported as illustrating the difficulties that may arise in the identification of such tumours. I strongly suspect that the lesions represent secondary carcinosis, but no primary could be discovered to account for them.

Case 4 (*Equine*, 10423).

The subject was an aged thoroughbred bay mare in poor condition. From the autopsy description(⁵) one learns that an extensive tumourous growth involved the pericardium, epicardium, heart-base, and the entrance to the thorax, extending into the neck and infiltrating the musculature of the latter (Figs. 107, 108). The growth involved also the pectoral and cervical musculature which show a speckled appearance due to numerous small whitish areas. Some grape-like growths were present on the diaphragmatic pleura. The ventral aspect of the sternum was affected by a large tumour-like growth, greyish-white, of cheese-like consistence. At the thoracic inlet, and extending back several inches, was a large tumourous growth causing flattening of the trachea and thrombosis of the blood-vessels (Fig. 107). The left lung was displaced dorsally by the pericardial growth, which was described as resembling cauliflower-like granulations and covering the whole of the left lateral, cranial, and caudal aspects and affecting also the epicardium. In the neck, the tumour was seen to extend as far as the larynx dorsal to the trachea, and the thyroid gland was firmer than normal in consistence. There were dilatation of the right auricle, pulmonary oedema, thrombosis of the great veins at the thoracic entrance and a marked

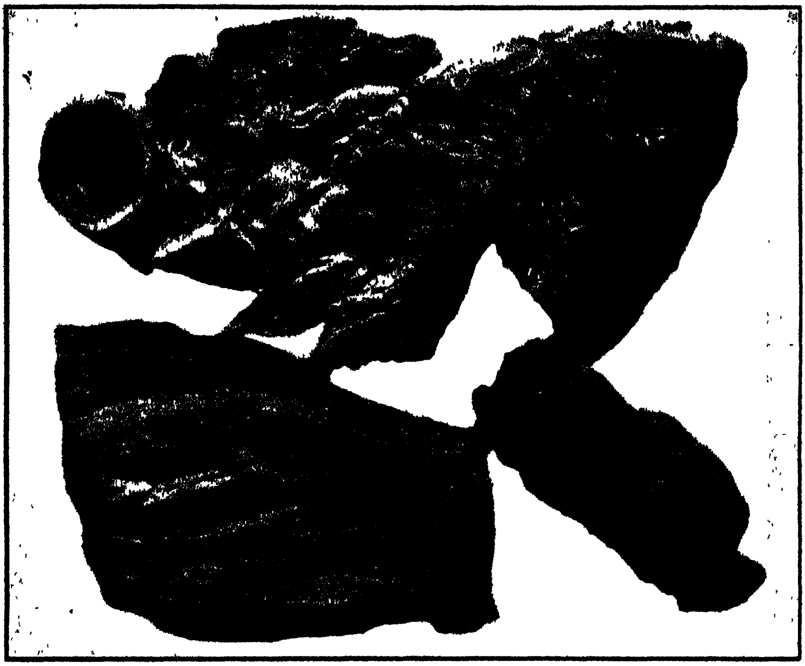

Fig. 107.—Pleural mesothelioma (?) of the horse: Invasion of cervical and thoracic musculature and (left, above) a mass of neoplastic tissue related to the trachea and bifurcation of the carotid trunk at the thoracic entrance. (10423A; 1/3×).

(⁵) Made by Dr. J. Quinlan, of this Institute.

oedematous swelling extending from the sternal region to the head, as well as to the thoracic and abdominal walls. (During life the animal had presented a hippopotamus-like appearance due to oedema associated with obstruction of the great veins from the head.) The cervical lymph-nodes were enlarged. All thoracic and abdominal organs were negative regarding the presence of a primary tumour which might have explained the extensive affection of the pericardium and pleura.

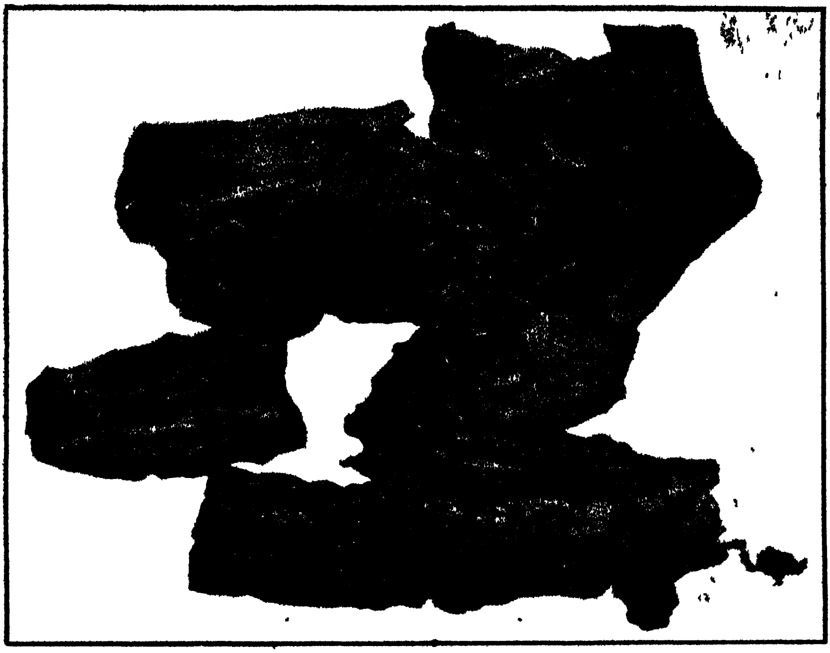

FIG. 108.—Further lesions from the same case as fig. 107 : Multiple plaques and grape-like growths on the pericardiac pleura. (10423B ; 1/3×).

Microscopically (Figs. 109, 110, 111, 112), the neoplastic tissue consists of a fibrous stroma containing nests of highly anaplastic cells: these are most variable in size 12μ to 30μ), have weakly basophilic to distinctly acidophilic, finely granular cytoplasm, are of polygonal shape, and often are tightly packed together in epithelial fashion without-intercellular stroma. The nuclei are extremely variable in size, from 8μ to 22μ in long diameter, and vary in shape from short-oval or almost spherical to long-oval. Further, irregularities in shape are common, and angular, lobed, and spindle-shaped nuclei are seen. Typically, the nuclei would appear to have the following structure: they are amblychromatic (vesicular), with a fairly delicate nuclear membrane (recorded as being intermediate in distinctness between that of a typical endothelial and that of a typical epithelial nucleus) and an exceedingly delicate and inconspicuous chromatin network; there are one or two (sometimes 3 or 4) extremely prominent nucleoli, the n : N ratio seldom being less than 1 : 25 and reaching 1 : 5. The above described morphology applies to the majority of the cells but there is much nuclear hyperchromasia, acidophilia of the cytoplasm, etc., interpreted as degenerative changes, and many of the cells with shrunken dark nuclei might be mistaken for a small lymphocytic type of cell. In places there is necrosis with a rich neutrophile infiltration. There may also be vigorous organisation of necrotic areas and replacement by granulation tissue. In a number of instances the masses of tumour cells can be seen to lie within lymphatic vessels of the subserosa and along these a rapid and widespread extension is obviously taking place. There is extensive invasive growth into the neck musculature and in the cervical lymph-nodes. The latter (Fig. 109) present an interesting picture, the lymphoid tissue having almost entirely disappeared and the lymph-cords and nodules appearing as inconspicuous, compressed remnants, while the entire sinus system is completely occupied and widely distended by the tumour cells. The latter are either loosely arranged, appearing to be simply drifting along the lymph-channels, or they form more compact masses which in section appear not unlike sheets of stratified epithelium.

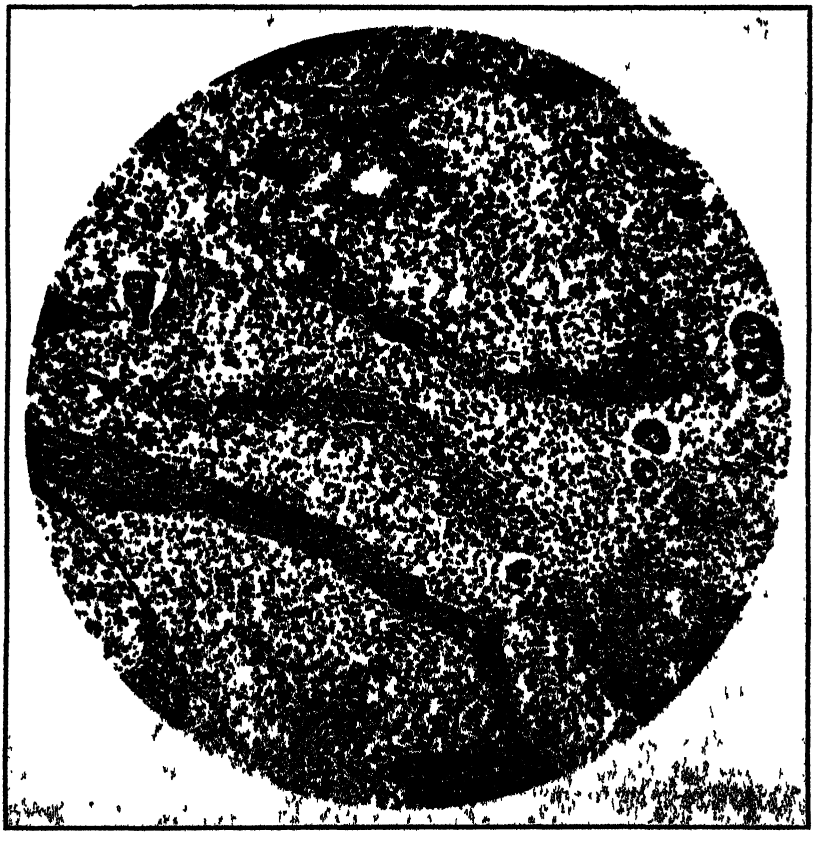

FIG. 109.—Metastases of pleural mesothelioma (?) of the horse in lymph-node: Loosely arranged tumour cells in the sinuses (between which are the atrophying medullary cords); here and there formation of gland-like lumina. (10423; 60×).

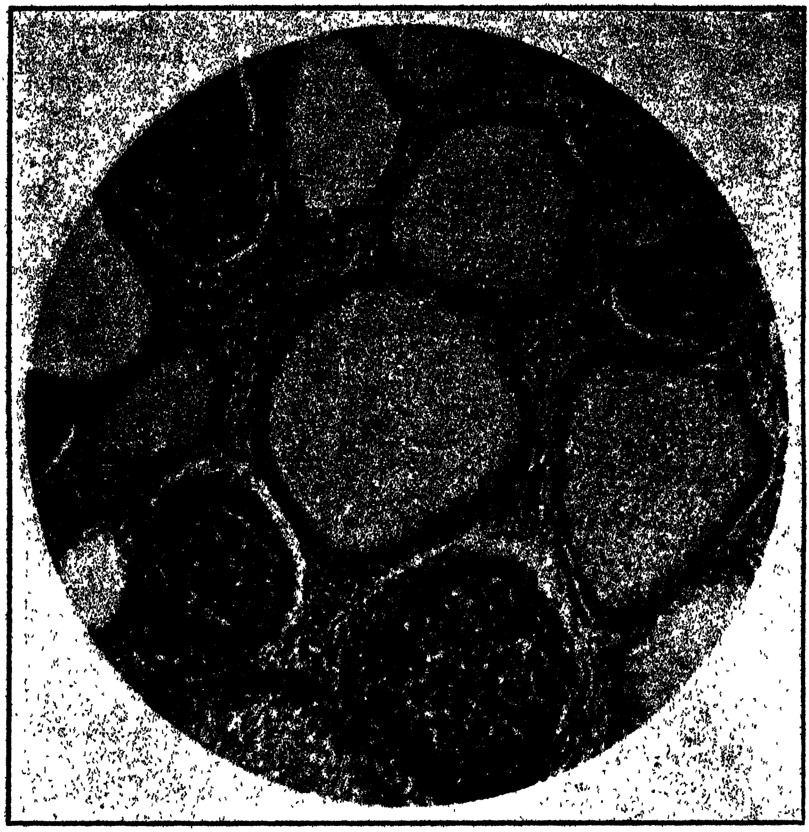

FIG. 110.—Pleural mesothelioma (?) of the horse (same case as figs. 107 to 109): Solid type of growth in the lymphatics of the interacinar stroma of the thyroid. (10423; 240×).

Sections through the pleura (Fig. 111) at the edge of the pleural growths show that in this region the mesothelial cells become mobilised, columnar in shape, often multi-nucleate and hyperchromatic, often with distorted nucleoli and an increased n : N ratio (1 : 25). In other words they resemble quite closely the less anaplastic of the tumour cells (Fig. 112). The subserous lymphatics are uniformly distended with masses of tumour cells. Some of the nodules are subserous and covered with hyperplastic serosal cells, in others the appearance is that the mesothelial cells have become neoplastic and merged with the tumour cells. In other nodules no clear alveoli occur, the cells being arranged in elongated narrow parallel cords between strands of cellular connective tissue. Such nodules may actually be naked, ulcerating into the pleural cavity. Sections of the thyroid show that the interfollicular stroma contains numerous centres of the same neoplastic growth, occupying and distending the lymphatics (Fig. 110). The mitotic index is 4.

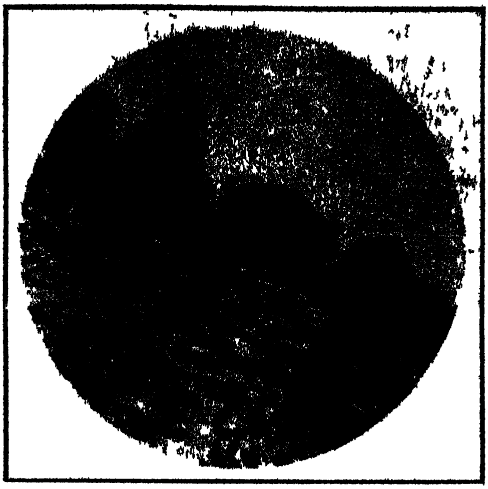

FIG. 111.—Mobilised cells of the pleural mesothelium at the edge of a pleural mesothelioma (?) of the horse. (10423. 950×).

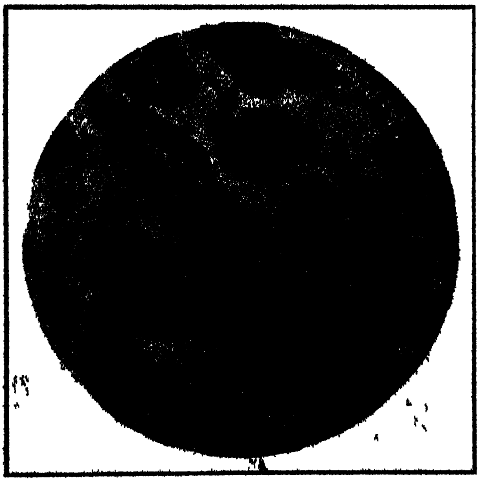

FIG. 112.—Detail of the cytology of pleural mesothelioma (?) of the horse: Resemblance of the neoplastic elements to the mobilised mesothelials shown in fig. 111; a band of the stroma runs through the centre of the field. (10423; 950×).

Remarks.—This neoplasm shows a degree of cell anaplasia comparable with the most rapidly growing of carcinomas and indeed the carcinomatous appearance of the neoplastic tissue is very striking. In this case however we have reliable autopsy data that no primary carcinoma occurred which could explain this tumour as secondary. Further, the picture seen of mesothelial mobilisation is highly suggestive, although I do not consider it in itself proof of a mesothelial origin; it may, on the other hand, be nothing more than a collateral hyperplasia and such appearances of continuity as are seen may be " false ", i.e. without histogenetic significance. On a close analysis of the cell morphology, discounting the anaplastic and degenerative changes, a fairly clear resemblance to the cells encountered in the bovine mesotheliomas is perceived, but here again caution is to be exercised in drawing inferences from a mere cytological similarity. We have here to deal with a highly malignant neoplasm which extends by intralymphatic growth, permeating the subserous lymphatic plexus of pleura and pericardium and growing in solid fashion along the tracheal lymph ducts, filling out the sinus system of the (cervical) lymph-nodes encountered, and extending also (in retrograde direction) into the lymphatics of the thyroid stroma. One would not here speak of typical lymphatic metastasis (i.e. depending on embolism) so much as of a direct extension against the direction of the lymph-stream within the lymphatics, the phenomenon being of the same nature as the " vascular transportation and generalisation . . . without local metastasis " reported by Oertel (1935). The diagnosis in this case, especially in view of the fact that there are no other equine cases in the collection for comparison, must be considered as very uncertain as compared with the other cases described; were it not for the assurance that a careful search was made at autopsy for a primary lesion, one would unhesitatingly identify the lesions as secondary to an undiscovered primary carcinoma.

Diagnosis.—Mesothelioma of the pleura? or pleural carcinosis (with widespread intralymphatic transportation) secondary to an undiscovered primary.

It is not desired to comment further on mesothelioma of the horse in view of our experience being confined at present to only one certain case; except to remark that in this species mesothelioma has been encountered only in the pleura and pericardium and that in our experience the pleural tumours proved to be far more vigorously growing and more rapidly extending than are the bovine peritoneal mesotheliomas. It is only by a close analysis of the cell morphology that resemblances to the structure of the bovine tumours are seen. It has in common with those tumours the property of almost exclusive intralymphatic spread.

CHAPTER VII.

Tumours of Connective Tissue.

A. Benign Tumours.

(1) *Fibroma* is an uncommon tumour of domesticated animals in South Africa. I encountered only three cases, but eliminated a very large number of lesions from this category, considering them to be slowly growing or regressing tumours of the sarcoid or papillomatous type (see Chapter X). The cases encountered comprise a soft fibroma (*F. molle et haemangiomatosum*—" nasal polyp ") of the horse, and fibromas of the skin of the dog and the external ear of a sheep respectively. In view of the great frequency of the lesions which are to be described in this work as equine " sarcoids ", great caution should be exercised before diagnosing fibroma of the superficial parts of the body in horses: such a diagnosis will convey a very erroneous impression to the clinician if it happens that he is dealing with a contagious and recurrent tumour. Similarly care should be exercised not to diagnose as fibromata of the skin bovine lesions which are really infectious papillomata with a predominating development of the connective-tissue moiety. The fibroma of the skin of the dog (15904) is not of this type, being covered by unaltered epidermis. It is to be considered a rare tumour.

(2) *Myxoma* was somewhat more frequent than fibroma. It is interesting that the only two cases in equines affected mules (in the same stable and at the same time). These lesions were situated subcutaneously. A fibromatose myxoma affected the neck of a sheep and two cases of myxoma were found in fowls (breast and wing respectively).

(3) *Lipoma* was a more frequent tumour than either of the preceding, 12 cases being encountered. In the horse and the ox the peritoneum was usually affected. A case in the sheep is the congenital lipoma of the meninges reported by Curson (1933). Lipoma was also found in the dog, but was not encountered in birds. Although Fox (1923) has reported a number of cases of lipoma in wild birds, this tumour must be rare in fowls. No satisfactory reports of simple lipoma in this species have been traced in the literature.

(4) *Chondroma* was as rare as fibroma. The three cases encountered affected the external ear of a horse and the ribs and sternum respectively of oxen. All therefore may be considered as enchondromas.

(5) *Osteoma.*—Four cases occur in the collection. Two affected the horse and occurred in the fascia lata and in the gum of the mandible respectively. The latter was a peculiar tumour which will be described in detail. The other two cases affected the cervical portion of the spinal column of an ox and the body of the mandible of a sheep respectively. Multiple bony enlargements of the gums of the dog were considered to represent exostoses probably arising on the basis of chronic inflammation rather than true osteoma. Similar bony protruberances have been mentioned as accompanying acanthoma of the buccal mucosa in this species.

(*Equine*, 11317).

The specimen (Fig. 113) consists of the body of the mandible of an aged horse. There is a flattened rounded enlargement of the gum in the space between the right lower canine and the corner incisor, measuring 5 cm. in diameter. Medially it reaches the middle line. Its central part is uncovered by mucosa and presents a reddened although smooth surface.

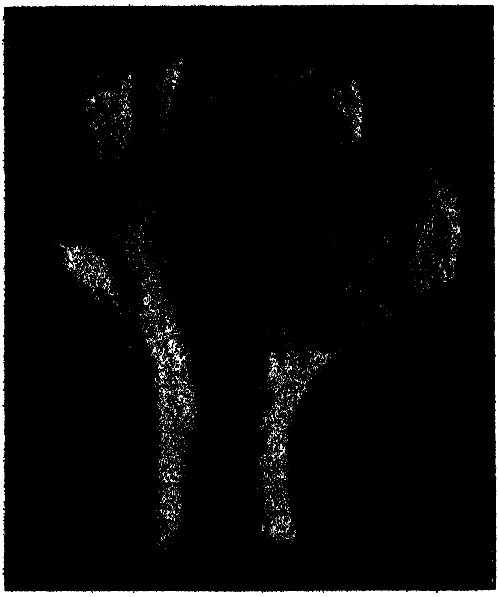

FIG. 113.—Osteoid osteoma of the gum of the mandible in a horse. (11317; 1/2×).

Microscopically this tumour consists of a dense collagenous stroma which is rather acellular but which in many places is infiltrated by plasma cells and scanty eosinophile leucocytes; throughout this are embedded thick branching trabeculae, usually appearing rounded or oval in transection, of a substance which is interpreted as atypical osteoid tissue: it stains bright red with van Gieson and through it course in a radial direction hyaline collagenous bundles continuous with those of the stroma. Within the substance of these osteoid masses are included cells resembling osteocytes, not arranged in any pattern whatever and usually present in scanty numbers. The osteoid structures are bordered by a row of vertically arranged cells (corresponding to osteoblasts) in intimate continuity with the fibrocytes of the stroma. In places there occurs a limited calcification of the central parts of the osteoid-like tissue; but on account of the sparse cellularity and the lack of pattern there is no recognisable resemblance to typical bone. Superficially the tumour is covered near its margin by the acanthotic epithelium of the gums, while centrally there is ulceration associated with a heavy eosinophile and plasma cell infiltration. Mitotic figures are absent.

Remarks.—This tumour had been thought to be an adamantinoma, a variety of tumour very rare in domestic animals and not represented in this collection. But such tumours are usually enclosed within the jaw and they rarely form enamel, for which this atypical osteoid tissue was mistaken; (the products of adamantinoblasts would, of course, stain with picric acid, not with acid fuchsin, being epithelial derivatives). This tumour is clearly of purely mesenchymal origin and although, microscopically, it presents an unfamiliar picture, its general nature is clear, viz. an osteoma of the osteoid type; this osteoid tissue is, however, of somewhat unusual appearance and in its lack of Haversian systems and of regular pattern it recalls the cement substance of the teeth.

Diagnosis.—Osteoid osteoma of the gum. The neoplastic tissue may possibly be regarded as an atypical formation of dental cement.

(6) *Osteochondroma.*—Only one case (15063) of such a tumour was found. It affected the dura mater of a fowl and compressed, without invading the brain.

7. *Note on Neurofibroma with a Report of its Occurrence in the Fowl.*

The collection contains nine specimens of false neuromata or neurofibromata from bovines. As the pathology of these lesions is well known (see Joest, 1920, *Bd.* II, pp. 624-628) in the ox, they may here be dismissed with the following remarks:—The following have been the situations of the tumours encountered in this country in bovines: *brachial plexus*, 3 cases, in one of which also the *heart* was affected; *intercostal nerves*, 1 case; *sciatic nerve*, 1 case; *tongue*, 2 cases: It was found that in the case of affection of the tongue by these multiple white nodules in the musculature the real nature of the lesions had not been recognised in routine diagnosis, although cases of the disease affecting this organ have been reported by Bossert (1910) and the condition is probably not to be regarded as a rarity. In two of our cases the site affected was not stated. It must further be pointed out that in no less than four of the cases were demonstrable, microscopically, intranuclear "inclusions" similar to those which have been described in other tumours as of nucleolar origin; in such cases there was also present a certain degree of cellular anaplasia which might be held to justify the term "neurosarcoma", but no direct evidence of a malignant type of growth was obtainable.

I know of no report of this disease apart from in Mammalia, and it is therefore interesting to place on record a case of which the domestic fowl was the subject:—

(*Fowl*, 8602.)

The subject was a Plymouth Rock hen sent in with the history of a few months' illness, the owner having noticed an erection of the feathers of the neck by which attention was drawn to the presence of nodules in the skin. The specimen consists of the skin (Fig. 114)

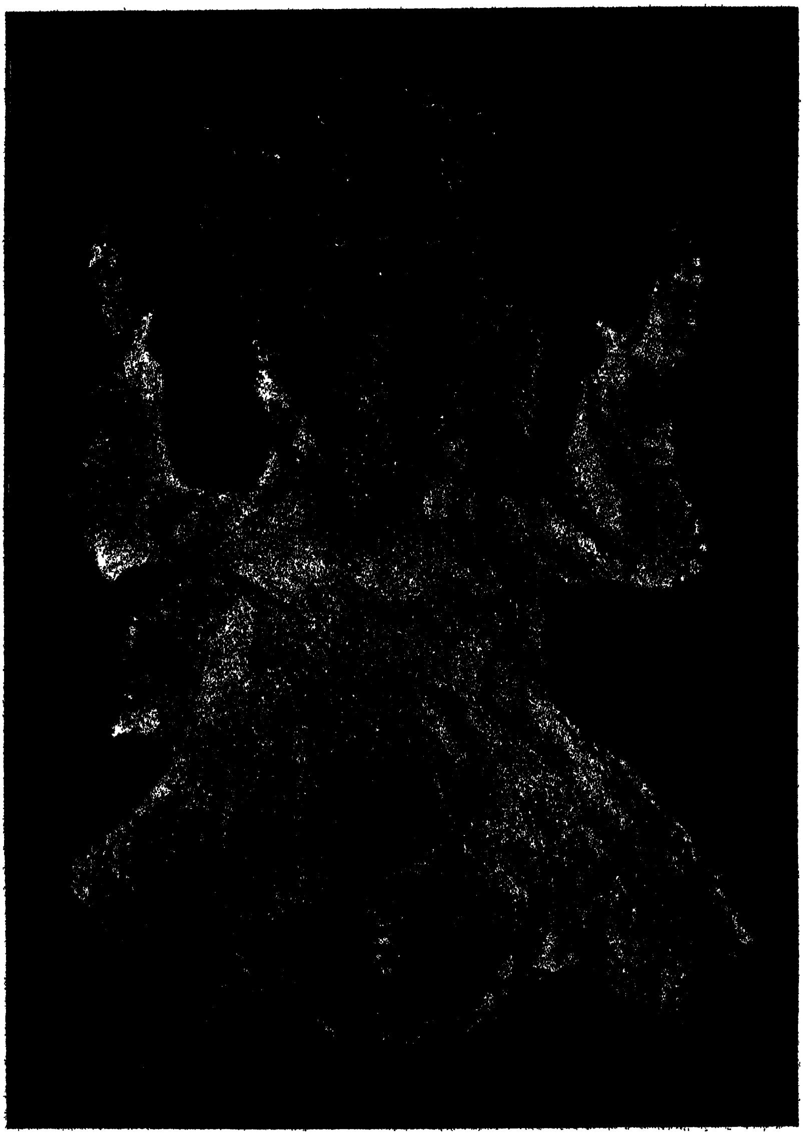

FIG. 114.—Cutaneous neurofibromatosis of the fowl: the largest nodules occur in the cervical region. (8602; 1/3×).

which bears very numerous nodules having a tendency, especially in the neck region, to produce considerable enlargements by confluence; thus the neck is completely encircled by a raised plaque of nodules which measures 11 cm. across (*elephantiasis neuromatosa*). The single nodules are irregularly scattered over all parts of the body, measure mostly 3 to 4 mm. in diameter and are seen to be closely associated with the mouths of the feather-follicles.

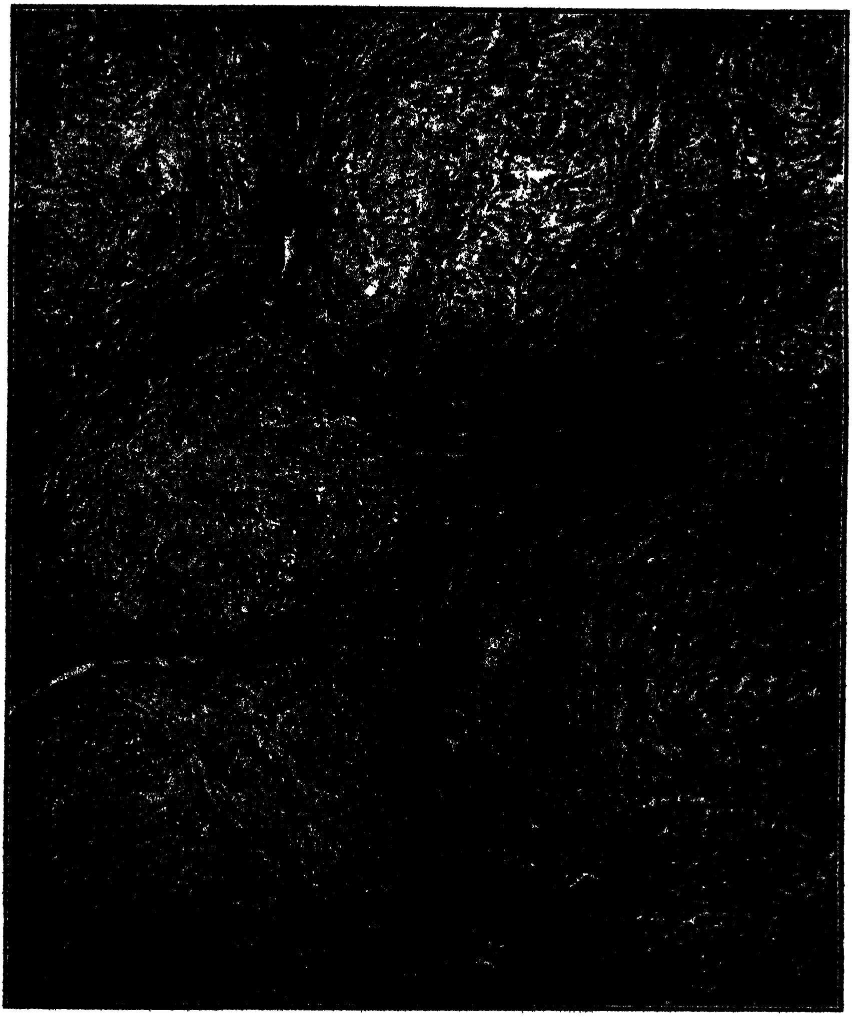

FIG. 115.—Structure of cutaneous neurofibromatosis of the fowl: Whorled arrangement of fibroblastic elements with tendency to myxomatoid growth in the centres. (Compare with the structure of mammalian neurofibroma). (8602; 100×).

Microscopically, the nodules are seen to be thinly encapsulated and to occupy the *cutis vera*, extending also into the subcutis. The tissue has a very characteristic appearance (Fig. 115). A collagenous fibro-cellular "stroma" with blood-vessels divides the "parenchyma" into regular rounded areas composed of loosely arranged, spindle-shaped and stellate cells of the fibroblast type associated with a loose intercellular feltwork of reticular and collagenous fibrils. The centres of these areas have a somewhat myxomatoid appearance. There is no cellular anaplasia and mitoses are absent.

Remarks.—Diagnosis is based on the multiple (primary) distribution, the not dissimilar gross appearance of the lesions to those of Recklinghausen's disease of man, and the characteristic microscopic picture resulting from proliferation of the endoneurium in rounded fascicules surrounded by the fibroblastic elements derived from the perineurium and which form a "stroma" for the former.

Diagnosis.—Cutaneous neurofibromatosis.

On enquiry was elicited the interesting fact that shortly after this hen had died, a cock on the same farm became affected by identical lesions, which likewise proved fatal. It is not known whether the two birds were related or not.

B. SARCOMA.

The term sarcoma lacks precise definition and is used by a number of different authors in almost as many senses. In general we understand by sarcoma a malignant tumour composed of elements of the connective tissue type; and while there is general agreement that fibrous, mucoid, lipoid, cartilaginous, and osseous tissues are of this type, the desirability of including the elements of the blood and blood-vascular system and of the haemopoietic tissues under the category of connective tissues is open to question. There has thus become evident a tendency to exclude from the scope of sarcomas malignant tumours of endothelial, muscle and glia cells and of the precursors of the blood-cells. Here we limit the application of the term sarcoma to the malignant counterparts of fibroma, myxoma, lipoma, chondroma and osteoma, known in the older literature as fibro-, myxo-, lipo-, chondro-, and osteo-sarcoma respectively. There is, however, a type of tumour long known as "mixed-celled" sarcoma, which also very properly falls under the category of sarcomas. As will be seen from studies of this tumour type in the bird, our opinion is that the cell type here concerned is the macrophage and its transitional grades to the fibroblast.

As we have previously had occasion to note, it is desirable to reserve the compound names in tumour nomenclature for the mixed tumours, and there is to-day a growing tendency to avoid the older nomenclature mentioned above. Thus fibrosarcoma(1) is replaced by the term fibroblastic sarcoma or (better still) fibroplastic sarcoma, chondrosarcoma by chondrogenic sarcoma, osteosarcoma by osteoplastic or osteogenic sarcoma. This practice could well be extended to give us the terms lipogenic and myxogenic sarcoma by which to denote malignant tumours of myxocytes and lipocytes respectively.

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(1) Even the older term fibrosarcoma is the subject of great confusion, having been used in two different senses: (*a*) to denote any fibroplastic sarcoma (e.g. Mallory); or (*b*) restricted to describe those fibroplastic sarcomas in which fibre formation reaches a high grade and predominates over cell multiplication, i.e. in more slowly growing tumours somewhat approaching fibroma in morphology. Such tumours would stand in contrast to "spindle cell" sarcoma, a term which lays stress on the predominance of cell multiplication over fibre differentiation

Of sarcomas in this narrower sense, the Onderstepoort collection contains 37 specimens, of which in 10 cases the position of the primary tumour had not been recorded. Between the varieties of sarcoma these specimens are distributed as follows: fibroplastic 15, mixed-celled 17, myxoplastic 2, osteogenic and chondrogenic 3.

1. *Fibroplastic Sarcoma.*

Fibroplastic sarcomas were found in 1 horse, 4 oxen, 1 sheep, 2 dogs and 7 fowls.

The structure of fibroplastic sarcoma is well known, but perhaps there is no other class of tumours in which such great difficulties of diagnosis and nomenclature occur. In general these neoplasms are composed of a stroma of blood-vessels which supports fibroplastic, spindle-shaped cells. The degree of collagen production varies greatly, so that all gradations exist between the slower-growing, highly fibrous "fibrosarcomas" and the very cellular "spindle-celled sarcomas" with limited fibril production, always however detectable with the special connective-tissue stains. On account of the fact that not only cells of the fibroblastic type but also epithelial and endothelial elements may assume a spindle shape, it is essential to apply such stains in all cases in which the diagnosis is not obvious. These stains further serve to distinguish in tumours smooth muscle cells, which when accompanied by a considerable amount of collagen may not otherwise be detected. This assumption of a spindle shape by other cells is responsible not only for difficulties but also for actual controversies regarding the nature of certain tumours. In human pathology the occurrence of spindle-celled tumours in the thyroid is well known and although most of these tumours are admitted to be atypical carcinomas by most authorities, there appears to be a lack of agreement as to whether sarcomas actually do or do not occur in this organ. In the Onderstepoort collection there is a lesion of the thyroid of a horse which might well be taken for a fibroplastic sarcoma if it were not possible by the application of fibrillar stain to show that from the tumour an intercellular fibrillar matrix is absent. It is especially for this reason—that neoplastic epithelial cells may assume a spindle shape leading to erroneous diagnosis of sarcoma (e.g. of the thyroid)—that the practical value of abandoning the term spindle-celled sarcoma is to be appreciated. Its replacement by the term fibroplastic sarcoma emphasises that the histological diagnosis is to be based, not on the shape of the cells, but on the evidence of their functional capacity to lay down an intercellular fibrillar matrix. Demonstration of this capacity of the cells must be held conclusively to exclude carcinoma, as least carcinomas of ecto- or entodermal origin; for collagen fibril formation is, by universal consent, held to be an exclusive character of cells of mesodermal, if not of mesenchymal, derivation. Theoretically, reliance should also be placed on the demonstration of the intracellular fibroglia fibrils of Mallory, but since special fixation (Zenker's) and a minimal post-mortal interim are essential for this technique, the point loses much of its practical importance. Intracellular fibrils may and do also occur in epithelial elements and for the diagnosis of fibroplastic sarcoma the final criterion must remain the demonstration of the production of collagenous or precollagenous (reticulum) fibrils by the tumour cells themselves, i.e. the *parenchyma* of the tumour consists of fibrils as well as cells, as opposed to tumours in which fibrils are confined to the stroma. Where stroma and parenchyma are poorly separated, as in some endotheliomas, or where, as in other endotheliomas, the tumour cells themselves produce reticulum and even collagenous fibrils as well, acute judgment and considerable experience of the interpretation of the reaction to fibrillar stains may obviously be needed to decide the diagnosis.

These difficulties are mentioned to emphasise my experience that the diagnosis and differential diagnosis of fibroplastic sarcoma is often far less easy than a perusal of the standard texts leads one to assume. And speaking of the domestic animals only, I wish to point to at least three dilemmas which have been encountered in the diagnosis of these tumours.

(i) The difficulties in the diagnosis of fibroplastic sarcoma in the horse—"*Sarcoids*": In the equine species in South Africa, tumours of the skin (subcutis) simulating or not readily distinguishable from fibroplastic sarcoma are frequently encountered. These growths are dealt with in Chapter X. They show much resemblance morphologically to sarcomas but lack extensive invasive powers, do not metastasize, and clinically give clear evidence that they are contagious. In this quandary, undesirable as it may be to multiply nomenclature, we have felt it wise to adopt the term "*sarcoids*" (already in use in human pathology), by which we may designate rapidly growing locally aggressive and recurring tumours which are composed of fibroblasts, but which do not metastasize and which do not exhibit microscopically the degree of cellular anaplasia which one expects to find in typical sarcomas. These lesions stand on the border-line between granuloma and fibroplastic sarcoma and serve to demonstrate yet again the familiar tenet that between chronic productive inflammatory processes and neoplasia a sharp distinction is often lacking. Ewing (1928) has mentioned, under the heading of presarcomatous lesions, " the occurrence of atypical inflammatory lesions leading to sarcoma ". He adds that " many sarcomas show such marked histological resemblance to inflammatory processes that many pathologists have long been inclined to accept in a certain sense the inflammatory . . . origin of sarcomas ". It is evident then, that dilemmas similar to the one under discussion have been encountered in human pathology.

(ii) The difficulties in the diagnosis of fibroplastic sarcoma in the dog: Here we wish to point to a case in which, from an autopsy, portions of the lung were submitted and found to contain multiple metastatic lesions having the histological structure of fibroplastic (" spindle-celled ") sarcoma. Before a diagnosis was returned the sender was requested to state where the primary lesion had been situated. On receiving the reply that the mammary gland had been affected, caution was exercised in framing the diagnosis: a return of " metastases of fibroplastic sarcoma to the lung " might naturally lead the sender to infer that a primary fibroplastic sarcoma of the breast had been responsible for the secondaries. It so happened that the breast tumour responsible for the metastases had previously been extirpated, although some time before and in another part of the country, and that the dog in question was identified as the subject of such a tumour which was already present in the Onderstepoort collection: this tumour was a mixed tumour (" carcinosarcoma ") of the breast in which, indeed, the spindle-celled sarcomatous element was by no means prominent and was not actually detected until a re-examination was made. The final diagnosis in this case was " pulmonary metastases of the sarcomatous moiety of a mixed (carcinosarcomatous) tumour of the mammary gland ". The distinction is perhaps not of great practical value, but from the standpoint of histological classification it would be unsatisfactory to overlook it. The case is interesting in providing an example of the " selective " metastasis of mixed tumours, the actual metastasizing moiety being the minor one in the primary tumour.

(iii) Difficulties encountered in the diagnosis of fibroplastic sarcoma in the fowl: In birds we have encountered a graded series of transitions between the so-called " mixed-celled " sarcomas and the fibroblastic sarcomas. Many of these mixed-celled tumours contain so great a preponderance of the non-spindle-shaped cells that it is highly desirable, histologically to classify them apart. Indeed, as will be mentioned later, the non-spindle-shaped elements may in certain cases be present to the virtual exclusion of neoplastic fibroblasts (spindle-cells) and it is obviously misleading to term such tumours " mixed-celled ". This difficulty is dealt with further under the mixed-celled tumours, where it is also urged that the cells mixed with the spindle-cells are actually neoplastic macrophages. It is therefore advisable to have at least two if not three categories whereby the microscopic appearance of these tumours can be conveyed, viz. fibroblastic, " mixed-celled " [i.e. fibroblastic and histiocytic (= macrophagic)], and histiocytic (= macrophagic) sarcomas. The difficulty arises, however, that there occur intergrades. This is to be referred, probably, to the ease with which the macrophage of the fowl [cf. the observations of Carrel and Ebeling (1926) on tissue cultures] can transform into the fibroblast, under as yet but little understood influences, a propensity which finds expression also in the neoplastic counterparts of these normal prototypes. Rous's (1910 and 1911) original fowl sarcoma was described by him as a spindle-celled sarcoma; yet in subgenerations (e.g. material from the South African Institute for Medical Research, through the courtesy of Dr. des Ligneris) this tumour could not be described otherwise than as a " mixed-celled " sarcoma. There is thus every reason to believe that spindle-celled tumours of birds can change into mixed-celled tumours, possibly even at different stages of their growth in one and the same individual: it is significant, in this regard, that Haddow (1933) has stated that the cells which first start to proliferate under the stimulus of the injected virus of the Rous sarcoma are actually the macrophages. It will be appreciated, then, that, although so far as possible we try to keep these histological classes of tumours apart, there are actually intermediate forms and that our morphological distinctions may well represent what is biologically an artificiality.

It is not proposed to report individual cases of fibroplastic sarcoma in this text. Perhaps the most unusual tumours were the sarcomas of the mouth and pharynx in bovines and that of the oesophagus in the dog.

2. *Lipogenic Sarcoma* (Liposarcoma).

This would appear to be a rare tumour and we have encountered no cases of it. In the diagnosis of such a tumour it would seem essential to distinguish two other conditions, viz. " embryonal " lipomas, cellular tumours with incomplete fatty differentiation but not to be regarded as malignant (two cases of such a tumour—from the dog and parrot respectively—have recently been added to the collection, but too late for inclusion here); and sarcomas in which the cells, having lipophagic activity, incorporate fat globules within their cytoplasm by an actual process of phagocytosis of the previously existing fat of the tissue that is being invaded. Such secondary fatty metamorphosis of the cell cytoplasm I have observed to assume striking proportions in the phagocytic (histiocytic) sarcomas of the fowl, and it is to be distinguished, as Borst (1902) has pointed out, from an essential tendency to fat-storing on the part of the tumour cells.

3. *The " Mixed-celled " Sarcomas, with Reports of Ten Cases in the Fowl.*

It is noteworthy that the " mixed-celled " sarcomas are the only kind of tumour for which no normal " type cell " is assumed. Ewing avoids the use of this term, merely mentioning that in certain cases " the tumour is highly cellular and reveals few traces of the original form and function of its cells, and in the most anaplastic types the cells are round and completely undifferentiated ". Henke (1906) uses the term " polymorphzellige Sarkom ". Mallory (1923), who gives a " type cell " for every tumour he discusses, makes no mention of these polymorphic celled tumours. MacCallum (1928) mentions tumours " in which cells of many forms and sizes occur, with many bizarre modifications of their nuclei. For want of a better term these may be called mixed-cell sarcomata ". It is evident, therefore, that some regard the mixed-celled sarcomas as mere anaplastic variants of the fibrosarcoma, that others avoid the difficulty by according them no mention, and that none venture to assign to these tumours a " type cell " or normal prototype.

Regarding this problem as it concerns the mammals, we shall have nothing to say, as almost all our tumours of this type occurred in fowls. That they are of frequent occurrence in this species is already known from the work of Malke (1930), who diagnosed over 66 per cent. of his specimens of sarcoma (including " lymphosarcomas, i.e. lymphoid leucosis) as " *sarcoma mixtocellulare* ". But a close description of these tumours in fowls is not to be found in the literature(²) and indeed it is by no means easy to assess what is the consensus of opinion regarding exactly to what degree a mammalian sarcoma must depart cytologically from the typical spindle-celled type before the term " mixed-celled " becomes applicable to it; here also there would appear to be intergrades.

We have encountered 15 of these tumours amongst poultry (14 fowls and 1 turkey). In four cases the ovary was primarily affected, in one case the wattle(³), in one the oesphagus, in one the breast, and in one the abdominal wall; in one case the site was not mentioned, and in the remaining 6 cases only metastatic lesions were submitted. Because these tumours lack precise definition and because in the routine examination at this Institute cases in which only metastatic lesions were submitted were baffling to the diagnostician, it is important to examine these neoplasms somewhat more closely than has been done in the past. Ten of these cases, which threw light on the nature and pathology of these tumours will be mentioned here.

Case 1 (*Fowl*, 14117).

The specimen consists of the wattle of a White Leghorn hen showing subcutaneously an ovoid tumour, 2 cm. in diameter and consisting of several lobes (some forming more or less distinct and separate nodules) of firm, whitish tissue; and the spleen of the same bird showing several poorly circumscribed white foci measuring up to ·5 cm. in diameter.

Microscopically, sections of the wattle tumour show this to be partially circumscribed; there are however outlying nodules of the tumour tissue. It is not truly encapsulated, although a condensation of the connective tissue of the deeper part of the *cutis vera* limits the growth to the subcutis; against this collagenous tissue the tumour shows expansive and not invasive spread. The neoplasm (Fig. 116) consists of irregularly arranged strands and nodules of spindle-shaped cells associated with a variable degree of collagen production, so that there are strands of fairly ripe connective tissue forming a kind of irregular " stroma " not separable from the rest of the neoplastic tissue and supporting large cellular centres and strands of two types:—(*a*) These consist mostly of irregularly arranged spindle-cells of the fibroblast type with but little fibril production and showing very restricted pleomorphism. Most of the nuclei do not differ in appearance of those of non-neoplastic fibroblasts and the nucleolar-nuclear ratios are not increased above normal limits. But there occur also multinucleate (true tumour) giant cells with short oval instead of elongate oval (or cigar-shaped)

(²) The work of McGowan (1928), in which these neoplasms are referred to as " tumours of the Rous type ", did not become available for consultation in this country until after this was written. My own conclusions regarding the " mixed-celled " tumours of the fowl agree substantially with his. On account of the closer cytological study here undertaken, the question of terminology, and the very poor illustrations which accompany McGowan's otherwise excellent book, I have decided not to modify this chapter of my work.

(³) Apparently! But as no complete autopsy protocol exists it is impossible to be certain that the wattle tumour was not a secondary one.

nuclei, having a definitely increased n : N ratio (e.g. 1 : 8), and showing submembranal hyperchromatosis. They possess up to a dozen nuclei. Occasional spindle cells also occur with considerably enlarged nuclei and increased nucleolar size. In these areas the cells are closely packed. (*b*) Rounded centres where the cells are scattered and which consequently present a very open texture. Here many of the cells assume a stellate form, having long processes. They are associated with the production of delicate bundles of collagen fibrils whose meshes are widely separated by a structureless medium apparently of the nature of an oedematous infiltration and not reacting as for mucin. The cells in these areas are more pleomorphic. Although the majority perhaps are still spindle-shaped, very many are definitely stellate. Their nuclei show greater anaplasia in the form of a definitely increased n : N ratio, which affects

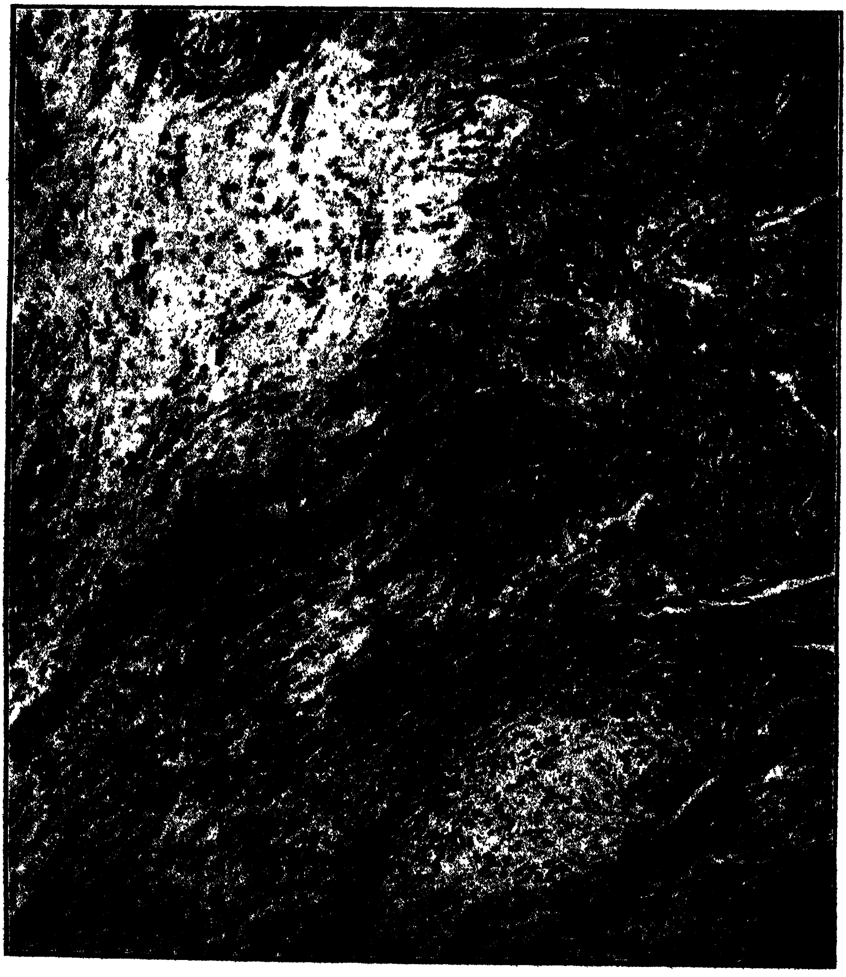

FIG. 116.—"Mixed-celled" sarcoma of the wattle in a fowl: Alternation of foci of loosely arranged neoplastic histiocytes with areas of neoplastic fibroblasts forming a denser tissue. (14117 ; 120×).

the majority of the cells, but more especially those that depart most from the spindle shape. These areas may merge into the denser areas (*a*) and there are all intermediate grades. Mitoses are not very frequent (M.I. = 1) and are rarer in the looser areas (*b*) which would thus appear to be, although " more anaplastic ", more slowly growing. There is a rich supply of thin-walled vessels constituting the stroma proper and often composed of endothelium only. In parts there is a very sparse " round cell " infiltration and in some of the looser textured foci was seen an infiltration of macrophages, having a large amount of " foamy " cytoplasm and compressed eccentric nuclei and not interpreted as tumour cells because of the absence of nuclear changes suggestive of malignancy. Here and there are actual foci of infiltrating lymphocytes.

In the spleen are multiple non-circumscribed foci of two types:—(*a*) In these the central portions much resemble the areas (*b*) of the primary, being composed of widely separated spindle and stellate cells associated with a meshwork of delicate collagen fibrils. But here the cells, especially as regards their nuclei, show increased anaplastic changes: many nuclei are greatly enlarged, irregular in size and shape, and have a greatly increased n : N ratio. Surrounding this central portion of the nodule and continuous with it is usually a peripheral zone of variable width, consisting of the typical neoplastic spindle cells: these are performing the actual invasion of the surrounding splenic tissue, the " differentiation " noted above taking place in the older central part. This peripheral rim may, however, be absent. Outside this zone, which is not encapsulated from it, is the splenic pulp, showing a pronounced infiltration of round cells and granulocytes contiguous to the advancing neoplastic cells. Mitoses are a little more frequent than in the primary, and are seen only in the peripheral zone. (*b*) These foci (Fig. 117) are poorly defined. Here the splenic pulp has not yet disappeared, but is permeated by a loose aggregation of bizarre cells which may be loosely grouped together or may actually appear (in sections) to be scattered among the elements of the white pulp of the spleen. These cells are of enormous dimensions (e.g. 75μ to 90μ commonly), and have a large amount of cytoplasm of quite irregular shape, and huge, bizarre, distorted nuclei; the latter are of vesicular type, with an inconspicuous chromatin network and with greatly enlarged nucleoli (n : N = 1 : 5) which may be modified in shape (angular, polyhedral). Only occasionally does one see the spindle-cell type with cigar-shaped nucleus, and in these cases the cells are also greatly enlarged, a giant spindle-cell resulting. Moderate fibril production is associated with these bizarre cells. The peripheral portion of their cytoplasm appears actually to merge into the intercellular bundles of collagen. (This point will be discussed later.) The cytoplasm often contains inclusions or vacuoles and in some cases actually phagocyted cells. Mitotic figures were not encountered among these cells, but nuclear constrictions suggestive of amitosis were seen. Fibroglia fibrils could not be demonstrated by Mallory's methods either in the primary or the secondary tumour (formalin fixation and post mortem interim). Bielchowsky impregnation also yielded no further information.

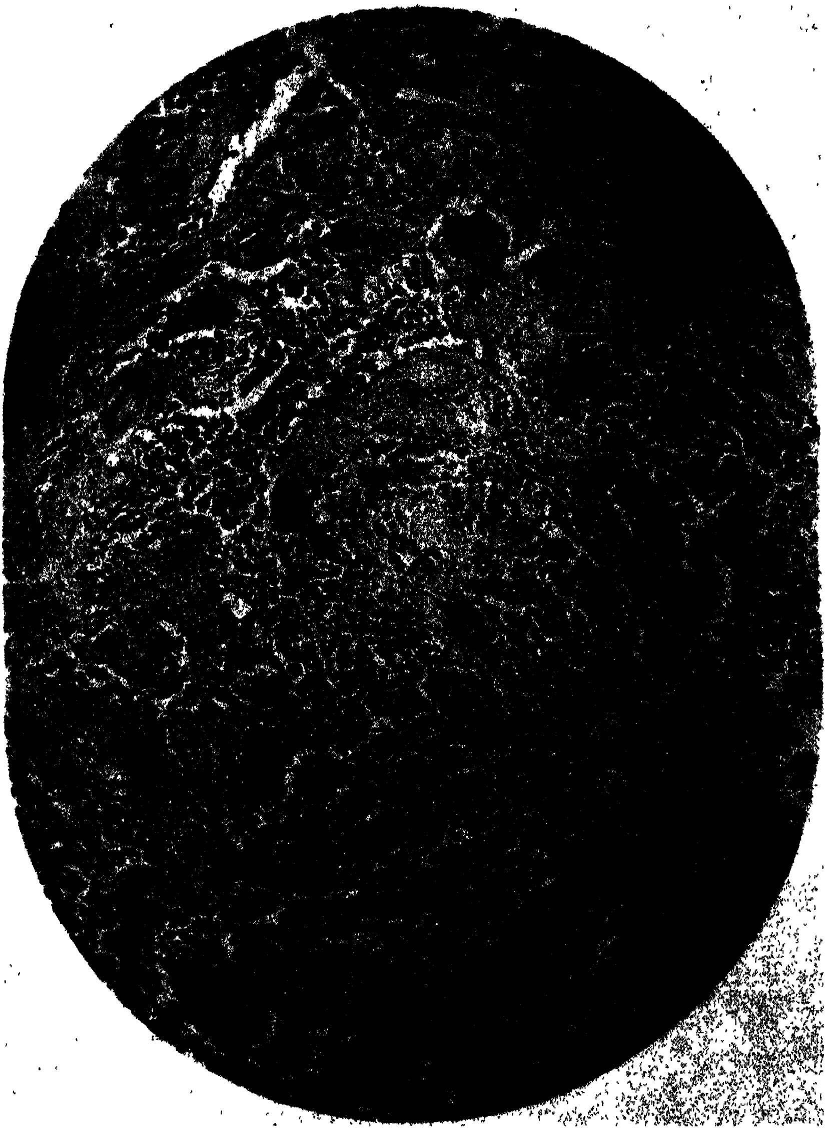

FIG. 117.—Splenic metastasis of the "mixed-celled" sarcoma of the fowl, shown in fig. 116: Invasion of the splenic pulp by large bizarre cells (histiocytes) the borders of whose cytoplasm undergo transformation into collagen. (14117; 260×).

Remarks.—The first sections of spleen which were prepared happened to transect only the nodules of the second type (with bizarre cells) and at that time great doubt was entertained that these foci were secondary to the wattle tumour, especially since metastases to no other organ had been reported—(the spleen is not considered a common site of metastases)—and the histological structure bore little superficial resemblance to the primary. Subsequent sections showed nodules of the first type in the spleen, thus demonstrating the grading of the bizarre cells into spindle-shaped fibroblastic elements and also showing clearly that metastases to the spleen had occurred. These less pleomorphic celled nodules show also a limited tendency to the bizarre morphology of a cell here and there, and close study showed even in the primary tumour a less exaggerated form of the tendency which is responsible for the same bizarre cell changes. Confirmation was obtained by the study of the other cases here reported, in some of which also the great variation in morphology between primary and secondary tumour came to be a familiar phenomenon. The pleomorphic celled foci have to be seen to recognise the difficulty of diagnosing such lesions without the experience which was gained later: cytologists and pathologists to whom the slides were shown could think of no resemblance of the bizarre cells except to nerve cells (large cell body, prominent nucleolus).

This case is of interest in two other respects. It shows clearly that collagen may arise intracellularly. Regarding this there has been a considerable controversy in the literature on histology into which I do not proposed to enter in detail (see Chapter I). The intracellular origin of collagen is supported by Mall (1901-02) and by the observations of Lewis (1917) in tissue cultures. The pictures to be seen in these tumour cells of the gradual fading of the cell border into the collagen fibrils are most instructive. Lastly the case is of interest in being the only avian tumour in the collection in which metastasis to the spleen occurred.

Diagnosis.—Fibroblastic and histiocytic(4) sarcoma (" mixed-celled " sarcoma) of the wattle(5), with metastases to the spleen, some of which grow as pure histiocytic sarcoma.

Case 2 (*Fowl*, 15161).

The specimen consists of portions of liver showing multiple, soft, white foci, fairly easily enucleated from the liver tissue, and meausring 2 to 5 mm. in diameter. There is no history or autopsy report.

Microscopically these foci are non-circumscribed and non-encapsulated, progressively encroaching on the surrounding liver tissue. They are composed of spindle-cells associated with rather sparse intercellular collagen deposition, and of much larger numbers of large

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(4) The justification of this term will be attempted at the close of the case reports.

(5) See remarks in footnote (4).

extremely pleomorphic cells (Figs. 118, 119, 120 and 121) having a most variable shape: rounded, polygonal, oval or elongated. They are characterised by a large amount of cytoplasm, and extremely bizarre, vesicular nuclei with very sparse chromatin network and usually a submembranal condensation of granular chromatin. The nucleolus is usually very large (n : N reaches 1 : 2) and the nucleus may be of almost any size or shape. Some nuclei are oval or rounded, but many are polygonal and some have extremely fantastic shapes. They may lie with their long axes across the breadth or shortest diameter of the cell (Fig. 121), thus well illustrating how far the latter has departed in morphology from the spindle-cell type. The cytoplasm often contains phagocyted inclusions such as leucocytes (Fig. 121) and especially fat globules (Figs. 119 and 120). Binucleate cells are commonly seen. Intergrades occur between these cells and those of the fibroblastic type first mentioned. A minority of the cells are quite small and rounded, not unlike lymphocytes, but their cytoplasmic rim is wider than a typical lymphocyte and the outline less regular. Mitoses are rare; usually only one can be found in a transection of an entire nodule.

Remarks.—The diagnosis of a case such as this presented extreme difficulty until experience was obtained of other similar cases in fowls showing a pleomorphic tendency of the sarcoma cells. The present case is one in which this pleomorphism is so exaggerated that recognisable cells of the fibroblastic type are greatly overshadowed and the bizarre cells attain a number and diversity of form superior to the other cases mentioned. It is possible that the primary lesion in this case, wherever it may have been situated, presented a less bizarre picture and would have been recognisable as a " mixed-celled " sarcoma. The present lesions are, however, predominantly of the macrophagic cell type and a mixture of the two cell types is detected only on close study.

Diagnosis.—Hepatic metastases of an unrecorded primary tumour probably having the morphology of a " mixed-celled " fibroblastic and histiocytic sarcoma. These secondary lesions are predominantly of the character of histiocytic sarcoma.

Case 3 (*Fowl,* 15427).

The specimen, sent " as a case of leucosis " consists of a length of about one foot of a fowl's intestine whose serosa and mesentery are studded with innumerable, white, non-encapsulated nodules varying in diameter from ·05 to 3 mm., while much larger masses result from confluence. These nodules have a pronounced predilection for the attached border of the bowel, where, extending onto the adjacent mesentery, there is a continuous diffuse thickening in which the limits of the individual nodules become very vague.

Microscopically, there are seen to be ill-defined, non-encapsulated foci in the mesentery and bowel subserosa consisting of rather loosely aggregated cells. Many of these are interpreted as neoplastic fibroblasts, but great pleomorphism exists. Many of the cells are spindle-shaped and associated with sparse intercellular collagen fibrils. Their nuclei are variable in size and may be cigar-shaped or of short-oval

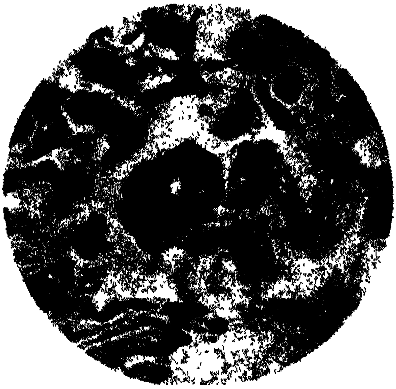

FIG. 118.

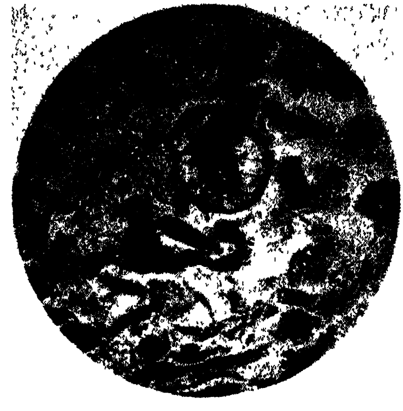

FIG. 119.

FIG. 118.—An anaplastic histiocyte in the hepatic metastasis of a mixed-celled sarcoma of the fowl: Irregularity of the nuclear outline and eccentric, enlarged nucleolus. (15161; 750×).

FIG. 119.—A neoplastic lipophage (macrophage) in the hepatic metastasis of "mixed-celled" sarcoma of the fowl: Note fat-vacuoles in the cytoplasm and compressed central nucleus. (15161; 750×).

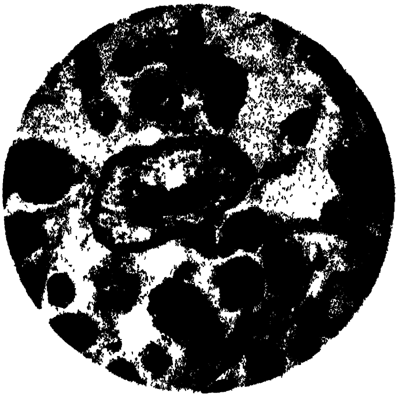

FIG. 120.

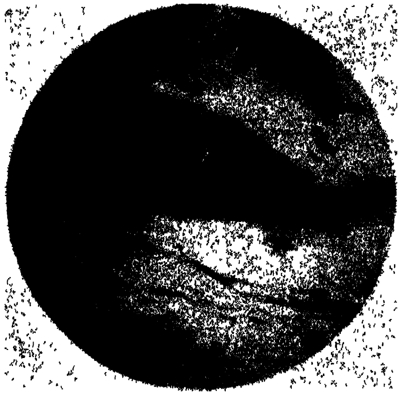

FIG. 121.

FIG. 120.—Neoplastic macrophage in the hepatic metastasis of "mixed-celled" sarcoma of the fowl: Foamy cytoplasm due to fat-vacuolation and compressed central nucleus. (15161; 750×).

FIG. 121.—Cytophagocytosis by a neoplastic macrophage in "mixed-celled" sarcoma of the fowl: Note the newly-phagocytosed leucocyte in the cytoplasm, the irregular nucleus and the enlarged nucleolus. (15161; 1150×).

shape; the nuclei are vesicular but have a heavy membrane. There is a scarcely visible, sparse chromatin network. The n : N ratio is increased, especially in the larger nuclei (e.g. 1 : 8). The nucleoli are one to two in number. There are from these cells all degrees of transition to large, branching cells with elongated cytoplasmic processes; they often have extremely large and bizarre nuclei, showing marked hyperchromatism. Of these cells, some are rounded up and contain many inclusions in their cytoplasm. Where the tumour tissue grows invasively in the mesenteric fat many of the cells are laden with (phagocyted) fat droplets. There also occur multinucleated giant cells apparently arising from multiple nuclear divisions. These may have about half-a-dozen small nuclei, most irregularly crowded together. Bi-nucleate cells are common. The tumour nodules are provided with a stroma of thin-walled blood-vessels usually consisting of endothelium alone, but over large areas these are few in number, and here necrotic centres occur. In parts the growths are limited deeply by the longitudinal muscular coat of the bowel, elsewhere actual invasion of this layer is in progress, although the circular muscular coat has not yet been reached. Mitoses were not seen.

Remarks.—These lesions have obviously arisen by transcoelomic implantation from an unrecorded primary. From experience (see the later cases) we know that the latter must almost certainly have been situated in the reproductive organs. The tumour cells are remarkable, in addition to their pleomorphism, for the pronounced phagocytic ability which they display, especially in respect of the mesenteric fat which they are invading. As mentioned (under the heading of lipogenic sarcoma) such neoplastic lipophages must not be confused for true neoplastic fat cells.

Diagnosis.—Transcoelomic implantations on bowel and mesentery of fibroblastic and histiocytic sarcoma; the primary lesion was presumably situated in the reproductive organs.

Case 4 (*Fowl*, 8487).

This specimen consists of the abdominal viscera of a hen. The various organs are matted together by a diffuse new growth consistng of innumerable confluent nodules which cover the mesentery (Fig. 122) and all other peritoneal folds. These nodules are mostly of irregularly spherical shape and vary in size from 1 to 5 mm.; but they are united by a more diffuse growth of the same nature, so that the whole mesentery is greatly thickened and presents a surface like that of a cauliflower; thus, large diffuse masses composed of a confluence of larger and smaller nodules on the mesentery may reach a diameter of 4 cm. and there are also present more discrete and more circumscribed masses of the size and shape of walnuts (oval, 2·5×2 cm.). One of these lies in the mesentery of the small intestine, and on its surface appear smaller nodules; another lies in the mesoduodenum at the proximal extremity of the duodenal loop, replacing the head of the pancreas. The rest of the pancreas is covered by multiple smaller nodules. A large diffuse mass occurs on the mesentery near its distal border but spreading from here to near the root of the mesentery. It measures 4 cm. across and spreads around the bowel wall, which it almost completely encases. The bowel is, in general, most affected along its attached border, but many nodules are also present on all other parts of the wall, where, however, confluence is less marked. The gizzard is solidly encased in a diffuse mass whose multiple nodular nature is still partly in evidence. The same is to be said of the proventriculus; and where this organ is related to the left lobe of the liver, multiple nodules occur on the liver surface. A portion of the oviduct and its ligament are present: both are affected by multiple nodules which, in the case of the ligament, incline to be diffuse; and, in the case of the duct, are relatively few in number, more discrete and scattered, reaching a diameter of 5 mm. Internally, the mucosa of this portion of the duct is unaffected. The spleen is intimately related and partially adherent to a diffuse growth on the peritoneum, but its capsule is intact and there is no invasion. The ovary contains a single fairly discrete growth, more or less spherical in shape and measuring 1·5 cm. in diameter. This is non-encapsulated, and deeply it comes into intimate relation with the ova while superficially it appears to be for the most part invested by serosa; at one part of its surface, however, the growth appears to have no serous covering. In the vicinity of this defect, large degenerate ova show a few scattered (implantation) nodules on their surfaces.

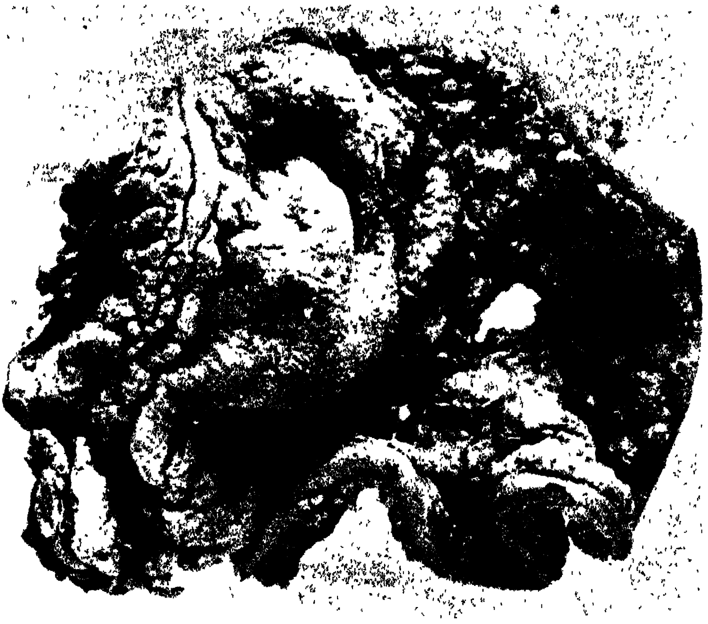

FIG. 122.—Extensive transcoelomic implantations on the mesentery and bowel serosa of "mixed-celled" sarcoma of the fowl (primary in the ovary). (8487; 2/3×.) (Reproduced through the courtesy of the Editor of *Farming in South Africa*).

Microscopically, the ovarian growth has an inconspicuous stroma formed entirely by thin-walled blood-vessels with but little connective-tissue backing. The parenchyma is composed of pleomorphic cells which are very loose in their arrangement and, unlike the cells of a typical fibroplastic sarcoma, show but a slight tendency to grouping in bundles. A close study of these cells enables one to establish two main types, and to see that probably the majority are of a nature intermediate between these types. (*a*) Spindle-shaped cells having a distinct similarity to fibroblasts and associated with the production of bundles of intercellular fibrils which react (although usually weakly) as for collagen with the van Gieson stain. These elements have vesicular, oval to cigar-shaped nuclei, which contain one or two moderately enlarged nucleoli. The nuclei are often modified to a cuboidal, rectangular, or pyriform shape. In some fields the tumour is composed largely or even exclusively of these cells which show a limited tendency to be gathered up into bundles, thus forming a tissue of denser texture than the other parts of the tumour. (*b*) In other areas, the parenchyma is composed almost exclusively of cells which are rounded, oval, or irregular in shape and which often possess cytoplasmic processes. Their cytoplasm is poorly outlined, stains a pink-mauve with haemalum-eosin and often shows single or multiple vacuoles (fat globules) which commonly attain a size of 10μ. Often, numbers of smaller vacuoles (1·5μ) may be present. These cells vary greatly in size, from about 14μ to as much as 52μ in diameter. Their nuclei are usually oval or spherical, sometimes bean-shaped in adaptation to the enclosed fatty globules. Occasionally they are pyriform, or irregular in shape. They may lie very eccentrically in the cytoplasm. They usually vary from 7μ to 13μ in diameter. In structure they much resemble the nuclei of the spindle-cells, being vesicular and having one or two nucleoli. The latter are usually somewhat larger than in the case of the spindle-cells, while in a minority of the cells a striking increase in the n : N ratio is seen (e.g. 1 : 4). The nucleoli are also often modified in shape: triangular or rectangular. In a number of these cells the nuclei show a slight condensation of chromatin in the submembranal zone, but on the whole hyperchromatic changes are not striking. In addition to the fatty vacuoles, the cells may contain a few acidophil cytoplasmic inclusions. These are spherical, do not stain much more brightly than the rest of the cytoplasm, have a hyaline appearance, and reach a diameter of 5·6μ. They consist of the remains of phagocytosed leucocytes. Bi-nucleate cells are fairly common and less often cells with three or more nuclei occur. The cells are not clearly associated with fibril formation: they lie somewhat isolated in the meshes of reticulum fibres. At the circumference of caseating necrotic foci occur many giant cells: large plasmodial masses having as many as 30 closely crowded nuclei not showing nucleolar enlargement and distinctly smaller than the tumour cell nuclei; these are considered to be " epithelioid " and foreign body giant cells of inflammatory and not of neoplastic origin. (*c*) A large number of cells are intermediate in type between types (*a*) and (*b*); i.e. they depart to variable extent from the spindle shape and become progressively less associated with the production of collagen fibrils. However there is still a fairly rich intercellular network of reticulum fibrils. (*d*) In limited areas, the presence of fatty vacuoles in the tumour cells reaches such proportions that the appearance of a lipoma is simulated. The whole cytoplasm becomes occupied by a large fat globule commonly measuring more than 50μ in diameter. At the periphery is seen the compressed, crescentic nucleus.

There is a moderate infiltration of granulocytes throughout the tumour. There are also large areas of fibrinous exudate with many (inflammatory) macrophages at their periphery. Deeply, the tumour lacks encapsulation, the infiltrating cells forming an indistinct margin and growing between the ova, many of which show signs of degeneration. Superficially, sections show that in parts the *albuginea* of the ovary resists the tumour invasion to some extent; in other parts only the serosa (germinal epithelium) remains intact. The mitotic index is less than 1.

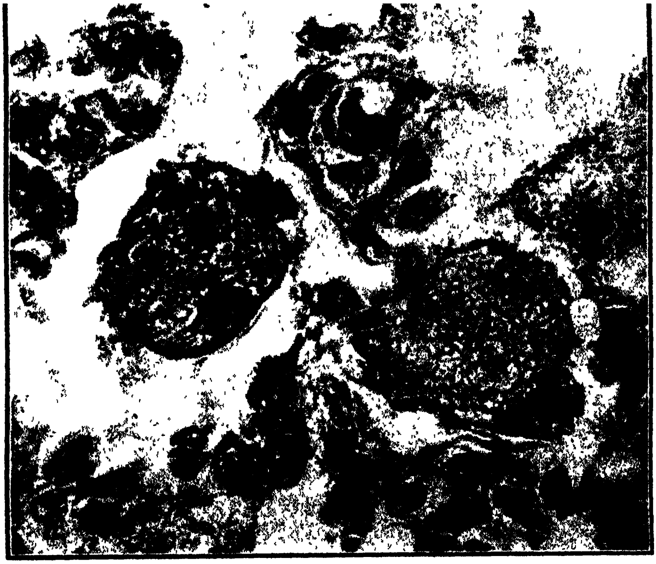

FIG. 123.—Large neoplastic macrophages in the mesenteric implantations of the "mixed-celled" sarcoma shown in fig. 122: Note the large amount of foamy cytoplasm due to phagocyted fat, and in the cell on the left also two phagocytosed cells in process of digestion. (8487; 750×).

The mesenteric nodules, while resembling the ovarian growth, show two main differences. The great majority of the cells (Figs. 5 and 123) are of type (*b*) (above), relatively few of the spindle-cells being present. Correlated with this is a greater sparsity of the intercellular reticulum. Secondly, there is a distinct increase in anaplasia; the average size of the cells is much larger, and a diameter of 60μ is commonly exceeded. Lipoid vacuolation of the cytoplasm is again frequent, but there is here a greater tendency for the whole or portions of the cytoplasm to contain multiple, closely-set, minute vacuolations (diameter *ca.* 1μ), conferring a honey-combed or foamy appearance on the whole or parts of the cell body. Examples of cytophagocytosis are also to be seen (Fig. 123). The nuclei also are on average much larger, and although the small ones are still often to be seen many reach a longest diameter of 30μ. Bizarre nuclear shapes are frequent and the borders may present a toothed appearance. There is a much greater tendency to hyperchromatosis and there may occur throughout the nucleus (and not only in the juxta-membranal zone) relatively coarse granules of chromatin, in some cases masking the vesicular nature of the nucleus. A number of nuclei are shrunken and look glassy and poorly stained. Most striking of all are the greatly enlarged nucleoli (see Fig. 5), measuring as much as 8·4 x 5·6μ, which often show bizarre alterations in shape (elongated, twisted appearance). A fair number of these nucleoli show various stages of a vacuole-like degeneration (discussed elsewhere) and minute vacuoles (Fig. 5) to large hyaline intranuclear inclusions may result. There is, however, no marked increase in the mitotic index in these implantation nodules. Large exudations of fibrin occur, again associated with an infiltration of macrophages; granulocyte infiltration is less marked and the greater part of the nodule is free therefrom. These nodules are seen to invade the mesenteric fat, penetrating intimately between the adipose cells. There is no encapsulation. They contain less collagen than the ovarian growth and their stroma is again formed almost entirely of thin-walled vessels.

The tumour from the mesoduodenum resembles more the mesenteric growths described than the ovarian tumour; although, as in the latter, there are present a fairly large proportion of spindle-cells, the large bizarre cells are numerous and show pronounced anaplastic changes. There are large, partially encapsulated foci of necrosis and haemorrhage.

Sections of small (pin-head sized) nodules from the wall of the apex of a caecum show the same tumour tissue with few spindle-cells and a majority of the large bizarre cells. These nodules occupy the subserosa and invade also the longitudinal muscularis, but not deeply. Larger (lentil-sized) nodules in the bowel wall are continuous with a diffuse growth invading the mesenteric fat and may completely replace the longitudinal muscularis and show commencing invasion of the circularis. In still other nodules the neoplastic tissue may penetrate as far as the *muscularis mucosae*, having completely destroyed the circular muscular coat. The (confluent) nodules in the mesentery are seen to lack serous covering, but to be joined by diffuse sheets of tumour tissue which are situated in the subserosa. Sections of the affected portion of the liver show that the capsule of that organ is intact and that the growth is confined to the subserosa. Anaplastic changes are not so marked as in the mesenteric tumours. Many infiltrating (inflammatory) elements are present.

Remarks.—This case had been diagnosed routinely as a " diffuse endothelioma of the peritoneum ", but whether this error arose on the basis of the observation of the thin-walled blood-vessels of the stroma (which are not, however, a striking feature) or in the sense of a mesothelioma was not stated. This diagnosis need not be seriously considered, since it was obvious that little attention had been paid to the cytology and that special fibrillar strains, other than van Gieson's, had not been applied. Further, the ovarian tumour had not been examined; it was treated as on a par with the other growths on the visceral peritoneum and, being considerably smaller than some of those, its primary nature was not realised. This case teaches well the principle that secondaries may often exceed the primary in size as well as in seriousness of their effects. It is clear from cases such as these, that difficulties are encountered in the accurate assessment of intra-abdominal tumours of birds. The safest criteria we can apply in these cases, in addition to our knowledge (based on experience) that the ovary or reproductive tract is *a priori* the most likely site of the primary, are those which depend on a minute study of the cytology whereby we may be able to recognise an increased anaplasia in the secondary as compared with the primary growth, as has been done in this case; enabling one to say with confidence that the ovarian tumour is primary and all the others implantation-metastases. The type cell of this tumour is the macrophage or histiocyte and its derivative the fibroblast. The cells tend to differentiate less in the direction of fibril formation than in the direction of the essential characters of the macrophage or histiocyte; this is seen in their pronounced phagocytic ability, their association (while still sessile) with reticulum fibres, and in other features of their morphology.

Summary.—A primary ovarian tumour composed of cells which, besides appearing as large pleomorphic elements showing, especially in respect of their phagocytic propensity, resemblances to the macrophage, tend to differentiate into elements of the fibroblast type. Both collagen and reticulum fibrils are produced and anaplastic changes are relatively slight. Extensive implantations on the mesentery and visceral serosae, forming diffuse growths by confluence and also more discrete growths which may exceed the primary in size. In these the tendency of the cells to resemble macrophages is much more pronounced and indeed the secondaries may be formed almost exclusively by such cells. Correlated with the secondary tumours is an increase in anaplasia, especially reflected in the nucleolar enlargement, distortions, and vacuolation. Yet the penetrative powers of the secondaries are limited. They tend mainly to form diffuse superficial sheets on the serosae; they may, however, as compared with the implantations of avian carcinomas, exhibit more infiltrative ability than is usual, invading the bowel as far as the *muscularis mucosae*. Lipophagy is marked wherever the tumours invade tissues containing lipoids—the ovary (yolks of the ova) and the mesentery (subserous fat deposits).

Diagnosis.—"Mixed-celled" (fibroplastic and histiocytic) sarcoma of the ovary, with multiple and extensive transcoelomic implantations to the serosae. The secondaries often grow an almost pure histiocytic sarcoma.

Case 5 (*Fowl*, 15100).

The following pathological anatomical findings were recorded at autopsy of a White Leghorn hen. Attached to the ovary by the visceral peritoneum is an oval, somewhat flattened neoplastic mass which lies compressed by the other viscera against the kidneys, on the ventral surfaces of which it causes an impression. It measures

4·5 × 4 × 1·5 cm. and is of a yellowish white colour. The surface is irregular and lobed and appears to be covered by the serosa except at the summits of nodular elevations. Its consistence is soft and the cut surface friable. In parts it is covered by a fibrinous exudate. The ovary also shows multiple, smaller, pedunculated tumours of the same appearance. The other viscera (proventiculus, gizzard, intestine, oviduct) show on their serous surfaces very numerous, often confluent nodules, varying in size from 1 mm. to 1 cm. The mesentery shows numerous discrete nodules measuring ·5 to ·7 mm. in diameter and there are also diffuse thickenings of the serosa due to confluence of such nodules. The free, as well as the attached, border of the bowel is affected in parts. The duodenal loop, mesoduodenum, and pancreas show the severest affection, confluence of nodules here producing extensive diffuse masses with cauliflower-like surfaces. The liver bears, superficially, tumour tissue which is continuous with omental implantations; elsewhere it shows pale, indistinct, poorly circumscribed foci of whitish colour. The kidneys are enlarged and their surfaces are affected by multiple, slightly raised, indistinct, pale foci ·5 to 2 mm. in diameter. Attached to the epicardium are a few pedunculated white foci, varying from 1 to 2 mm. in diameter. The oviduct has occasional nodules on its serosa, up to 7 mm. in diameter. The oviducal ligament bears more frequent but smaller nodules (2 to 3 mm.), which in places are confluent especially near the ovary, with whose tumours they also show direct continuity. The pancreas is much enlarged and invasion by tumours situated on its surface is to be seen.

Microscopically, the study is considerably hindered by fairly advanced autolytic changes. The large ovarian tumour consists of a delicate reticular stroma (not reacting for collagen) which supports indistinct alveolar-like groups of cells which are mostly of a polygonal shape, are closely packed and between which there are scanty intercellular fibrils. These cells have a finely granular acidophilic cytoplasm often containing vacuoles which react with Sudan III stain. They have oval to spherical nuclei with a distinct nuclear membrane and a single prominent nucleolus often lying eccentrically and sometimes modified in shape (elongated, slightly curved or bean-shaped). The nuclei appear to be of vesicular type and poor in chromatin, but their structure is often masked by autolytic changes and by karyorrhexis. A good many show hyperchromatic changes, especially an accumulation of heavy particles beneath the nuclear membrane. The cells are often closely packed in strands within which little intercellular fibrillar matrix can be detected. In parts they tend to be elongated and resemble the (spindle-shaped) fibroblast. Large masses and scattered globules of yolk lie scattered in the tumour tissue which has developed in and is clearly replacing the ovarian tissue. Penetration of the tumour cells into vascular lumina can be seen: the endothelium of such invaded vessels appears prominent and hypertrophic (collateral hyperplasia). Such vessels also contain free yolk. Superficially the neoplastic tissue is limited by the ovarian albuginea, which is covered by a deposit of yolk globules and fibrin and is infiltrated by polymorphonuclear granulocytes and macrophages ingesting the yolk globules; the germinal epithelium over the tumour has disappeared. Over large areas the tumour cells show necrobiotic changes (acidophilia, karyorrhexis).

The blood-vessels of the stroma are moderate in number and thin-walled. Invasion of them by tumour cells can often be seen. The mitotic index is rather low (index = 1).

The ovary itself is invaded by multiple unencapsulated foci of the same nature as the large tumour. In addition there are multiple foci of invading cells whose cytoplasm is filled with (specific) rounded granules most of which are eosinophilic and a minority of which are basophilic. These are identified as pseudoeosinophile myelocytes(⁶). They have oval or bean-shaped nuclei, which are of vesicular type and usually simple, although occasionally there is a tendency to the formation of not more than two lobes. Their nucleoli are not prominent and indeed in most of them no distinct nucleolus is to be seen. Both this and the previously described type of growth are causing destruction of the ova and in parts the two types become intermingled (" collision "). This second infiltrating tissue has a higher mitotic index than the first. Its cells are separated by a scanty reticular stroma. Masses of yolk globules lie scattered among the cells of both types of tissue. The ovarian lymphatics often show a prominent, hypertrophied endothelium and can be seen to contain neoplastic cells of both types as well as ovarian elements—yolk globules and follicular epithelium. Actual pictures of vascular invasion by the myelocytes can also be seen.

Sections of the mesoduodenum and pancreas show that the latter organ is everywhere closely invested by a neoplastic growth which invades the parenchyma only at certain points, being elsewhere resisted by the capsule, under which necrotic areas occur in the gland substance (interference with nutrition due to the close investment and effect on blood supply). The neoplastic implantations on the mesoduodenum are of the following types: (*a*) large foci of neoplastic myelocytes, (*b*) foci of cells corresponding to those in the large ovarian tumour, and (*c*) mixed foci similar to (*b*) which are actually also invaded by the myelocytes. The neoplastic tissue which actually invades the pancreas consists of distinct foci of types (*a*) and (*b*). In sections of the kidney the cortex shows multiple small foci of neoplastic myelocytes intimately invading the interstitium and destroying the parenchyma. The veins(⁷) can be seen to contain yolk and myelocytes; invasion of veins by myelocytes can actually be seen. The polychromatic reaction of the specific myelocytic granules can best be observed in this organ. The liver is hyperaemic and has focal infiltrations of the same nature as those in the kidney, The foci tend to be perivascular in location (portal veins). Myelocytes and also liver cells occur in the blood of the veins. Sections of this organ which transect the porta reveal extensive implantations of both types, often intermingled without definite demarcation (Fig. 124). The liver capsule resists the implantations of the ovarian growth (sarcoma) but is penetrated by the myelocytic neoplastic tissue which, to a limited depth, invades the underlying parenchyma (by direct continuity). The serosae show on their surfaces deposits of both types of neoplastic elements, blood-cells and yolk globules. The subserosa is invaded by both types of neoplasm, either one or the

(⁶) See p. 343 for the common errors in identifying such cells.

(⁷) Renal portal system!

other preponderating in different sections. Nodules on the oviduct and oviducal ligament consist entirely of the sarcomatous growth, which may invade the duct deeply, breaking through the mucosa, especially where the wall is thin (funnel region). Excellent examples of lipophagy on the part of the tumour cells occur in the subserosa of this organ. Sections of the heart (Figs. 125, 126 and 127) show two types of foci:—(*a*) These are in the minority and are of pin-point to pin-head size. They lie in the subepicardial tissue and from there invade between the muscle fibres of the myocardium for a short distance. They cause the overlying serosa to be slightly raised. These foci consist of myelocytes. In a blood-vessel close to such a focus a mass of yolk globules can be seen mixed with the blood-cells. (*b*) The majority of the foci are larger (e.g. 5 mm.). They consist (see Fig. 125, above) of rounded or polygonal cells varying in size from 4·2 to 12·5μ. They also lie in the epicardial subserosa, but may produce a prominent elevation or even be pedunculated without

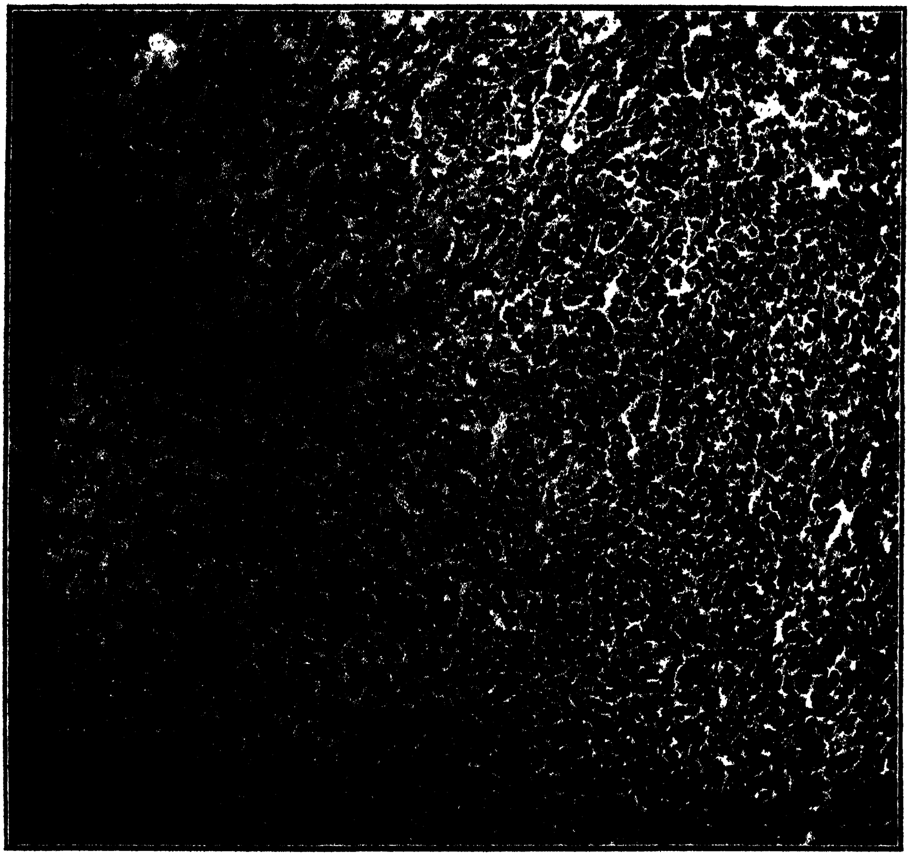

FIG. 124.—A collision tumour in the fowl: Left, histiocytic sarcoma and, right, myelocytoma intermingling in transcoelomic implantations to the serosa of the liver; both primary tumours situated in the ovary. (15100; 250×).

demonstrable serous investment. The closely packed cells lie in groups of oval or rounded shape and demarcated by strong trabeculae of collagenous tissue (i.e. there is here again an alveolar arrangement). The cells have a somewhat undifferentiated appearance, no polarity is recognisable, the nuclei may be single or double, measure 5μ to 7μ in diameter, and are often irregular (angular, pointed) in shape. The nucleoli are very large and prominent and often of oval

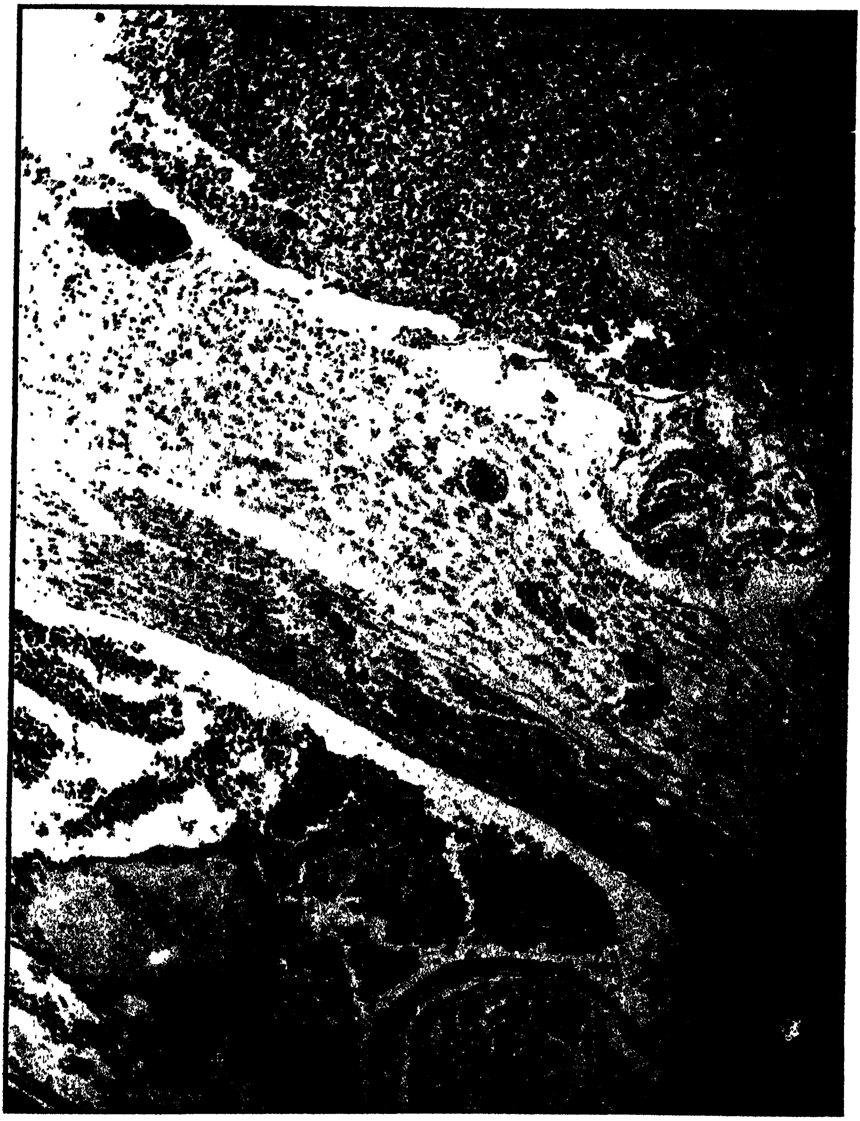

FIG. 125.—Epicardial metastases of histiocytic sarcoma of the fowl: Above, indifferent round-celled growth; below, invasion of veins by cartilaginous neoplastic tissue. (15100; 120×).

shape (n : N = 1 : 4). The cells are separated by delicate intercellular reticulum fibrils. Their cytoplasm is opaque, non-granular, dull mauve staining with haemalum-eosin, and fairly often contains one to six sharply defined (fatty) vacuoles, 1 to 3μ in diameter, often grouped to one side of the cell, exerting pressure on the eccentric nucleus. It constitutes a moderately broad ring around the nucleus, which is always somewhat eccentrically situated and of vesicular type, with a single, slightly to moderately eccentric nucleolus occupying a considerable part of the nucleoplasm. Occasional cells may be moderately elongated, with the nucleus situated at one pole. Many nuclei show karyorrhexis. These cells are undoubtedly of the same general type as those encountered in other " mixed-celled " sarcomas, although less bizarre.

A modification of these foci occurs in some which are imperfectly encapsulated (i.e. breaking through their capsules, or capsule deficient in parts) and are prominently pedunculated. They consist of cells as described above, but dispersed in a large amount of hyaline intercellular matrix (Fig. 126). This substance appears to have a shredded appearance (parallel lamellation, probably a post-mortem artefact) and reacts well with Hoyer's thionin stain, giving a distinct metachromatic reaction for mucin. The same arrangement of collagenous trabeculae is present, and these are continued as distinct reticulum fibres penetrating between the individual tumour cells in those parts which lack the hyaline matrix: for it must be explained that large groups of cells may occur in or around the edges of the masses of the matrix. Where hyaline matrix has been laid down, no fibrils can be seen. The cells in parts show a distinct tendency to be arranged in vertical rows and this appearance together with the hyaline matrix (which indeed is thought to represent a chondromucin) confers on the issue an appearance reminiscent of cartilage (Fig. 126). Further, in parts (Fig. 127) may be found, if a search be made, a fair number of cells in the matrix which show indistinct capsules reminiscent of the chondrin globes of hyaline cartilage. The tumour cells, where they become isolated in the matrix, often undergo a degenerative change whereby the cytoplasm becomes strongly acidophilic and finely granular; and finally the nucleus disappears and a blotch of acidophilic granular material is left in the matrix to mark the spot previously occupied by a cell. Breaking through of the neoplastic tissue into the lumina of veins can be observed in the epicardium and in the underlying myocardium, and in the veins in this vicinity masses of this neoplastic cartilage-like tissue can be seen (Fig. 125, below), while free tumour cells are often mixed with the blood. In parts the matrix of these nodules is channelled by cavities without lining endothelium and containing fresh blood-cells, apparently in circulation (Fig. 126). These channels often become irregular and widened into considerable lagoons of blood.

Remarks.—We have here to deal with a large primary ovarian tumour having the general morphology of a " mixed-celled " sarcoma, as is shown by the phagocytic and fibroplastic propensities of the cells. The anaplastic changes are somewhat limited and many of the cells would correspond with what in older pathological terms might be called " large round cells ". The alveolar structure, although not very distinct, led to a confusion with carcinoma when the primary tumour was first examined. The tumour cells are active in phagocyting the yolk globules set free in the destruction of the ovarian tissue. This process of yolk destruction reaches a degree where in the blood-stream in various parts of the body may be found circulating emboli of yolk globules. Evidence of the invasion of the blood-stream (and also possibly the lymph-stream) is seen in these sections. In the ovary itself there are multiple smaller tumour interpreted as local metastases (probably lymph-borne and retrograde?). These coexist with multiple foci of neoplastic myelocytes—myelocytoma (myeloid leucosis), and the two types of tumour

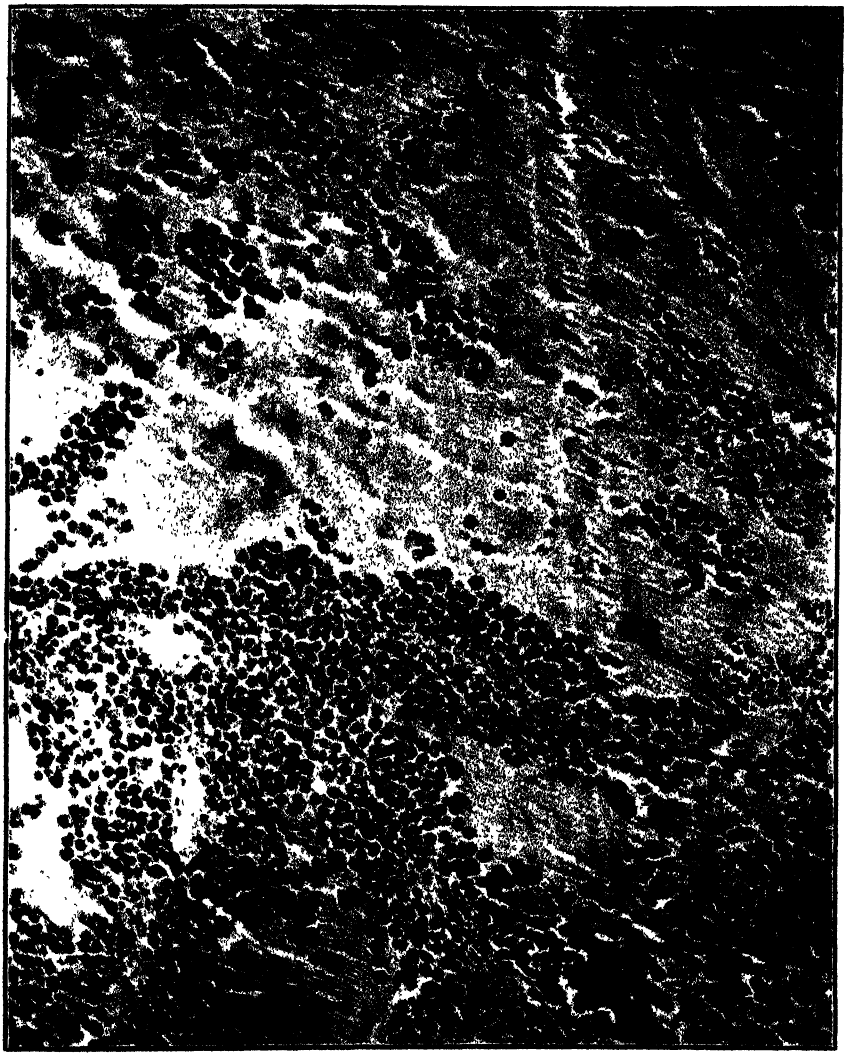

FIG. 126.—Epicardial metastases of "mixed-celled" sarcoma of the fowl: Round cells becoming dispersed in a (chondro-mucinous) matrix which is canalised by blood. (15100; 250×).

tissue often become intermingled by a process of collision during their growth. The myelocytomatous foci also invade the vessels, into which these neoplastic elements burst, carrying with them at the same time actual normal elements (yolk masses and follicular epithelium) of the ovary.

Further, there is extensive spread by transcoelomic implantation, the seeding from the ovary occurring on all the visceral serosae. Complicating this is a chronic peritonitis set up by the freed yolk and the (often necrotic) neoplastic elements. These implantations, affecting mesentery, bowel serosa, and liver serosa in both cases, and also the oviduct in the case of the sarcoma, reach their greatest dimensions in the mesoduodenum and on the liver serosa at the porta of that organ. The mesoduodenal growth so invests the pancreas as to cause focal necrosis of that organ (presumably through mechanical interference with its blood-supply) and both types of neoplastic tissue penetrate the capsule to invade the parenchyma. The (more resistant) liver capsule was found to have been penetrated by the myelocytoma only, and even this grew inwards only to a limited extent, by following the bile-ducts from the porta. The kidney and liver show multiple foci of myelocytoma which are dispersed throughout those organs and are not the result of implantations. In the oviduct the sarcomatous implantations show considerable invasive powers, penetrating as far as the mucosa. In the heart the most interesting changes are met with. Here the blood-borne metastases of the ovarian sarcoma assume a peculiar modification in which not only

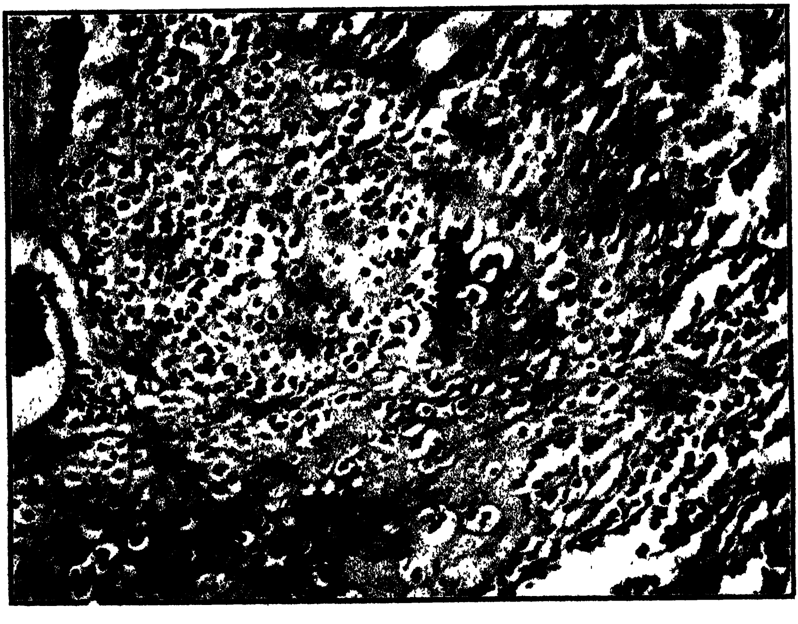

FIG. 127.—Another field of the sarcoma metastases shown in figs. 125 and 126: Enclosure of tumour cells in capsules suggestive of hyaline cartilage (chondro-sarcomatous growth). (15100; 250×).

may (in some foci) the cells remain in a less differentiated (and therefore less easily recognisable) state, but a differentiation occurs (in other foci) whereby an atypical cartilaginous tissue, having marked vascular invasive properties, occurs. These foci morphologically have to be described as chondrogenic sarcoma, although they are admittedly not typical of that entity. Considerable hesitation preceded their diagnosis as secondaries of the ovarian neoplasm. However, the fact that blood-borne metastases of this ovarian growth to the epicardium had actually occurred is proved by the non-chondrogenic epicardial foci, which actually establish a distinct morphological link between the structure of the primary tumour and the chondrogenic heart foci. This is further confirmed by the presence also of (blood-borne) metastases of myelocytoma in the epicardium. The circumstance that tumours were not recorded in the lungs need not concern us(*) since myelocytoma metastases in those organs were also absent and the finding of yolk globules in circulation in the heart shows conclusively that elements from the ovary *had* eluded arrest by the pulmonary capillaries. In spite of the fact that in some of these epicardial secondaries is deposited a (chondro-) mucinous matrix in which the cells become enclosed in the manner of cartilage cells, they are not necessarily regarded as an exception to the rule (itself, as we have seen elsewhere, by no means inflexible) that the secondary neoplasm does not show increased but rather decreased differentiation as compared with the primary; indeed these " chondrogenic " cells are in some respects—actual cell morphology—considerably less differentiated than the cells of the primary. Under what stimulus this urge to deposit mucinous matrix in the subepicardium arises I can offer no suggestion.

Diagnosis.—" Mixed-celled " sarcoma of the ovary (fibroblastic, but predominantly histiocytic) with local metastases in the ovary; implantations to the mesentery and visceral serosae with direct invasion of the pancreas from the mesoduodenum and deep penetration of the oviducal wall; blood-borne metastases to the epicardium tending to grow as chondrogenic sarcoma. Coexistent multiple myelocytoma (myeloid leucosis) affecting the ovary, kidneys, and liver, spreading by transcoelomic implantation from the ovary to the serosae, invading the pancreas by direct spread from the mesoduodenum and the liver from the hepatic serosa, and giving rise to (blood-borne) metastases to the epicardium. The two tumours not seldom come into collision, so that some of the foci are a mixture of the two types.

Case 6 (*Fowl*, 10403).

It is not possible to give a complete report of naked eye appearances in this case, as only fragments of some of the lesions were submitted and an autopsy report is not available. The specimen consists of the following material from a hen:—The ovary is the seat of multiple pedunculated and sometimes confluent nodules, varying

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(*) Willis (1934) emphasises that in man the passing of malignant neoplastic cells through the pulmonary capillaries without setting up lung metastases is to be accepted with caution. But the lungs of the bird are not necessarily comparable with those of mammals in this respect.

in size and shape: the smallest are irregularly spherical and about 1 mm. in diameter, while the largest tend to be oval and measure up to 2 cm. in diameter. They are intimately intermingled with the ova and the whole mass measures 6 × 3·5 × 2 cm. The cut surface, discoloured through preservation, was (probably) white in colour and it shows occasional dark haemorrhagic areas near the surface. The consistence is fairly firm. A detached mass measuring 3 cm. in diameter and having a partial serosal covering has apparently been cut away from the ovary. Fragments of kidney and skeletal muscle show tumour foci of similar appearance to those in the ovary. The spleen was reported to have been enlarged and no liver is available for macroscopic description (although there are sections of this organ).

Microscopically, the different ovarian tumour nodules vary considerably in appearance due to variation in the differentiation of their component cells. The neoplastic tissue intimately invades the ovarian tissue, surrounding and in parts replacing the Graafian follicles. The stroma proper is composed of thin-walled blood-vessels and is sparse. The parenchyma shows the following structure in different lobules: (*a*) spindle-shaped cells, rather loosely arranged and presenting the morphology of fibroblasts. They are associated with the production of collagen fibrils in moderate amount and these form an irregular feltwork permeating between the individual cells. In many lobules these fibroblasts, apart from their irregular arrangement, show no cytological indications of malignancy—the nuclei may be very uniform and changes in the chromatin and in the nucleolar size may be absent. In such parts of the tumour mitotic figures cannot be found. (*b*) A loose arrangement of large cells often measuring 50μ or 70μ in long diameter and having the most irregular shapes. Some are polygonal, others triangular, irregularly spindle-shaped or rectangular as seen in section. They often anastomose with their neighbours by means of broad cytoplasmic processes. Their cytoplasm is large in amount and in the sections it has a dense appearance, staining a deep reddish-pink to pink-mauve with haemalum-eosin; it appears finely granular on highest magnification and often contains somewhat more acidophilic areas or globular inclusions. Often it is vacuolated throughout and the vacuoles, especially the larger ones, are situated for preference in the peripheral portion of the cell. The individual vacuoles vary greatly in size, from the limit of visibility to about 7μ. They are usually rounded or ovoid but may be of irregular shape. Only one or two large vacuoles may be present in a cell or there may be a number of vacuoles of variable size arranged near the cell border, or innumerable minute vacuoles may confer a reticulated or foamy appearance on the entire cytoplasm. The cell borders are usually very distinct, being partially or wholly outlined by a fine, fibril-like, cuticular condensation, staining more intensely than the rest of the cytoplasm (collagen fibrils intimately associated with and apparently resulting from a condensation or transformation of the border of the cytoplasm). The nuclei tend to be eccentric and are often placed at the extreme edge of the cell with little or no cytoplasm enclosing their outer aspect. They are most often single, even in the largest cells; but many cells have two nuclei, and multinucleated cytoplasmic masses (3 or 4 or more nuclei) are commonly to be seen. The nuclei vary greatly in size and shape: in general they tend to be oval and some are spherical; many departures from this shape are seen—markedly elongated (spindle-shaped), bi-lobed or dumb-bell, pyriform, semilunar, kidney-shaped, and wholly irregular nuclei. The smaller oval nuclei may measure only 5·5μ across, while the larger ones may measure 35μ, the average long diameter being about 11μ. Typically the nuclei are distinctly vesicular, there being a scanty chromatin reticulum within a moderately sharp nuclear membrane. Within this palely-staining nucleus the greatly enlarged nucleolus is a conspicuous object. It is usually single, less often double, seldom triple. The majority of these nucleoli are spherical, but variations in shape are common; oval, cigar-shaped, pyriform, and angular nucleoli are encountered. Their outlines may be blotchy, as if the nucleolar material were diffusing into the nucleoplasm. They may show central vacuolation or rarefaction, as described elsewhere. They may be placed very eccentrically, against the nuclear membrane, or may lie more centrally. In diameter they measure as much as 7μ and n : N ratios of 1 : 3 were recorded. In the nuclei, hyperchromasia is a frequent change and this may mask the typical vesicular appearance, especially when the whole nucleoplasm becomes filled by coarse chromatin particles; or the particles may accumulate beneath the nuclear membrane leaving a clear central zone. Occasional nuclei are shrunken and pycnotic. Mitoses are not frequent; some of the figures are abnormal (giant chromosomes, etc.). The index is less than 1, even in the most rapidly growing parts. The tumour cells in these areas are supported by a rich stroma of blood-vessels associated with a small amount of connective tissue, from which scanty fibres penetrate between the individual cells. With the van Gieson stain, in occasional cells irregular globules are seen to be present, reacting for collagen; or fine fibrillar strands of the same material appear intimately associated with and sometimes definitely forming a part of the "ectoplasm" as described previously. (*c*) In the ovarian sections a structure intermediate between (*a*) and (*b*) is not so well seen as in the muscle metastases to be described below. Moreover, in some of the lobules composed predominantly of fibroblast-like spindle cells, amoeboid elements of the same general appearance as those characteristic of areas (*b*) occur. In some areas a rather regular alternation of bundles of spindle cells and collagen fibres with enclosed groups of polygonal cells results in a (pseudo-) alveolar appearance, not to be mistaken for carcinoma. Or the free, polygonal elements lie intimately mingled with the spindle cells; they do not reach so large a size as in the areas (*b*), although their nuclei may be multiple. They usually measure 8 to 9μ in diameter. Their cytoplasm takes a similar deep stain, but instead of being granular it has an opaque, hyaline appearance and the vacuolation is not a prominent feature, although occasional vacuoles may be seen. In general, in these areas there are distinct signs of anaplasia as compared with the areas (*a*), although not comparable with areas (*b*) in this respect: nuclear irregularities occur fairly frequently in the spindle cells, especially those appearances suggestive of amitotic divisions, and elongated, lobed, and twisted forms are to be seen. In occasional nuclei there appears to be a moderate nucleolar enlargement as compared with the non-neoplastic fibroblast. The free polygonal cells do not however show the bizarre nuclear changes described above, their nuclei being small, spherical or slightly oval and having very moderate sized nucleoli. Their cytoplasm may contain distinct globules reacting for collagen. In one nodule, consisting chiefly of spindle cells with a few polygonal cells and in which there is more collagen formation than elsewhere, occur rounded, circumscribed foci of stellate, branching elements, widely separated in a (semi-fluid) matrix through which run fine fibrils—a typically myxomatous transformation.

Mitoses are not seen in these areas. The free surfaces of such nodules may show a distinct encapsulation arising as the thickened ovarian *albuginea*. In other cases the tumour is limited superficially by a more-or-less unaltered subserosa over which the germinal epithelium is still intact. The latter may show proliferative downgrowths into the ovarian stroma(⁹).

In parts there is a moderate granulocyte infiltration.

In all these different parts of the ovarian tumour, the blood-vessels are crowded with cells of the lymphoid haemoblast type, which often greatly preponderate in numbers over the contained erythrocytes. Among these cells mitoses may occasionally be seen (lymphoid leucaemia).

In the kidney, large areas of the parenchyma are replaced by a destructive tumour growth resembling most the areas (*c*) above, and in which spindle cells predominate. Mitotic figures are not seen. The blood-vessels in these sections are again crowded with haemoblasts.

Sections of the voluntary muscle submitted show tumour foci composed mainly of spindle cells having fairly distinctly enlarged nucleoli and hyperchromatic nuclei, and with occasional free cells approaching the type described under primary foci (*b*). These nodules are clearly transitional between areas (*a*) and (*b*), and the free-lying tumour cells show less marked distortions of the same nature as those previously described. In some cases the growths are limited by the fascia associated with the muscle, in others distinct invasion of the muscle fibres is in progress.

The liver, in the sections available, discloses a replacement of large parts of its parenchyma by extravascular proliferations of cells of the lymphoid haemoblast type. These cells also invade the sinusoids and all the blood-vessels are packed with similar elements mixed with the circulating blood.

In the spleen a diffuse replacement of the normal pulp by lymphoid haemoblasts is seen.

Remarks.—Here again we have to deal with a tumour which is primary in the ovary. The (recorded) metastases are blood-borne and occur in the kidney and skeletal musculature. In structure the tumour again consists of cells of the fibroblast type, showing cell

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(⁹) Apparently a reversion to the embryonic potentiality of forming sex-cords (cf. Fell, 1923-24 and Popoff, 1931).

gradations into foci which are almost purely composed of the large bizarre cells with which the previous cases have made us familiar. As in the previous case, in some foci the alternation of bundles of cells specialised more in the direction of collagen fibril-production with groups of polygonal elements leads to an alveolar appearance of some parts of the tissue which may be confused with a carcinomatous type of growth. In this tumour, as in Case 1, a close study of the appearances seen with the connective-tissue stains is instructive in demonstrating the fact that collagen may be formed intracellularly, in this case occurring as actual hyaline globules within the cytoplasm as well as in the form of fibrillar condensations of the edge of the cell body. The cells have largely retained this potentiality of matrix production in addition to the specialization as the foamy, lipophagic elements reminiscent of the macrophage. No clearer demonstration could be found of the transition to the fibre-forming fibroblastic cell type from the mobile phagocytic type, because here intermediate grades can be seen to an extent not possible in the normal prototypes of these cellular elements. What is especially interesting is this " abortion " of the collagen forming propensity whereby, instead of supporting fibrils, (useless) masses of collagen develop within the cytoplasm. Co-existent with the sarcomatous affection is the well-known avian disease lymphoblastoma (lymphoid leucosis) which in this case is accompanied by a lymphoid leucaemia resulting from invasion of the blood-stream by the neoplastic lymphoid cells.

Diagnosis.—" Mixed-celled " (fibroplastic and histiocytic) sarcoma of the ovary, with blood-borne metastases to the kidneys and skeletal muscles. Coexistent lymphblastoma (liver and spleen) with invasion of the blood-stream (lymphoid leucosis with leucaemia).

Case 7 (*Fowl*, 12007).

No macroscopic description can be given. The sections of ovary show an invasive growth composed of fibroplastic spindle cells, and, greatly predominating over these, free cells which show marked lipophagic activity. Much free yolk lies scattered among these tumour cells and large haemorrhages are common. The n : N ratio reaches 1 : 9 in some cells, but in general the bizarre nuclear changes previously noticed are less pronounced, although the nuclei are often distorted and compressed in the periphery of the cells by the pressure of the fat globules in the cytoplasm. Mitoses can be found, but are rare. The sections of the intestine show mesenteric implantations at the attached border of the bowel which to a slight extent invade the longitudinal muscularis. Except that the secondaries are even more haemorrhagic than the ovarian tumour tissue, their structure is identical.

Remarks.—This tumour was erroneously diagnosed as carcinoma. The error arises from the misconception that carcinoma is the only ovarian tumour of fowls giving rise to implantations and from the mistaking of the fibroplastic spindle cells and their fibres for a " stroma" supporting the " parenchyma " of polyhedral cells; in reality of course all the cellular elements of the tumour are neoplastic, the true stroma, as before, consisting only of blood-vessels.

Diagnosis.—" Mixed-celled " [fibroblastic and (predominantly) histiocytic] sarcoma of the ovary, with mesenteric implantations.

Case 8 (*Fowl*, 8206).

This specimen consists of portions of the oesophagus, which at one point is the seat of a pronounced enlargement. This is occasioned by a spherical tumour (Fig. 128) measuring 2·5 cm. in diameter, which ulcerates through the mucosa and occupies the greater part of the lumen at this point. It presents an unencapsulated surface, and its outer part is a thick necrotic rind which on section is seen to be continued from a large necrotic mass occupying the centre of the growth. The tumour has a whitish-grey colour (Kaiserling preservation) and is fairly firm in consistence. Outwardly it penetrates through the oesophageal wall, and is firmly adherent to the trachea, which it partially encircles, causing a constriction of the lumen.

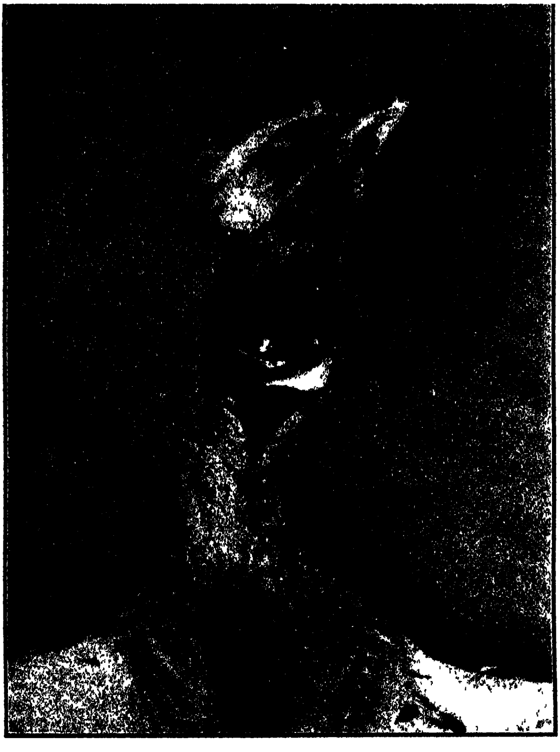

Fig. 128.—" Mixed-celled " sarcoma of the oesophagus of a fowl. (8206; 1/2×).

Microscopically, the oesophageal tumour replaces all the layers of the wall of this tube, invading and destroying the muscularis and also the mucosa, through which it ulcerates, presenting internally a free surface covered with necrotic debris and haemorrhagic exudate. The oesophageal lumen remains as a narrow circumferential slit. The tracheal sections show that although this organ is surrounded by the tumour, no actual invasion has taken place, there being here a weak encapsulation against the tracheal adventitia. The neoplastic tissue consists mainly of spindle-shaped elements resembling fibroblasts, but associated with little collagen production. These cells are arranged in ill-defined and often loosely aggregated bundles which run in all directions. The stroma is represented by scanty thin-walled blood-vessels with which is associated a small amount of collagen. The tumour cells are intimately associated with a rich stroma of reticulum fibrils (as disclosed by the two fibrillar stains of Mallory), and these react poorly or not at all with acid fuchsin. These fibrils form a rich network, of which the larger bundles run parallel with the cells, while the individual fibrils run in all directions between the cells and appear intimately associated with their cytoplasmic borders. The tumour cells are mostly plump, spindle-shaped elements, whose boundaries are indistinct, but which often measure some 25μ in length. Their cytoplasm is rather large in amount and shows a very finely granular structure with the phosphotungstic acid haemaeosin stain (no fibroglia fibrils being demonstrable, although after long preservation in formalin and Kaiserling this would hardly be expected). They have vesicular, oval to spindle-shaped nuclei, in which one, two or three large nucleoli are prominent. The latter are often oval (e.g. 4·2 × 2·8μ) and the n : N ratio may be 1 : 6·5. Besides the above elements, there occur throughout the neoplastic tissue, but especially at its infiltrating edges (where they actually preponderate), larger cells usually having a stellate shape but often also irregularly rounded and lying quite free from their neighbours. These elements present a distinctly bizarre appearance owing to the many distorted shapes which their nuclei are apt to assume and to the great prominence of their nucleoli. These distorted nuclei are connected by a series of transitional grades with the oval or elongate nuclei of the spindle cells, and all transitions between the two cell types occur. The large cells often measure 24μ in diameter (excluding their ill-defined cytoplasmic processes, when present). Their nuclei vary much in size: most are irregularly oval or rounded, many are kidney-shaped and not a few of bizarre angular or multilobate form; or they may be boomerang-shaped, lying very eccentrically in the cytoplasm: this eccentric position is associated with the presence of vacuoles in the cytoplasm, forcing the nucleus to the periphery. There are usually one or two nucleoli, but more may be seen; they are almost without exception greatly enlarged, and a great many of them show distinct changes in shape and staining reaction: oval, pyriform, and Y-shaped nucleoli are commonly seen. In many the staining is modified owing to a central rarefied area, which sometimes is so large as to occupy most of the bulk of the nucleolus (" inclusions "). Such vacuolated nucleoli especially are very large; they may measure 4·2μ in diameter, and the n : N ratio reaches 1 : 5·4. Two vacuoles may be seen in a single nucleolus or a number of minute ones may be present producing a morulate appearance most aptly to be compared with that of a typical Negri body in the nerve cells of the dog. In a number of cells the nucleolar material is blotchy, lightly staining, and seems to have fallen apart in a number of fragments of indefinite outline. Cells containing two or several nuclei may be seen, and the latter are often closely packed together, exerting pressure on each other: it is often difficult to decide whether a cell has a single multilobed or fissured nucleus or multiple closely-crowded nuclei. The cytoplasm of the cells much resembles that of the more spindle-shaped elements. Its peripheral part is intimately associated with a rich network of reticulum fibrils, but itself shows no fibrillar structure. In a number of the cells the cytoplasm appears more dense and opaquely staining. Occasionally a phagocyted cell (e.g. lymphocyte) may be seen within this cytoplasm. Mitoses are frequent at the growing edges and many of the figures are abnormal (triasters, giant chromosomes). Among the larger, bizarre cells the mitotic figures and abnormalities are especially frequent. The mitotic index is 2. The tumour is throughout infiltrated by lymphocytes and pseudoeosinophils, and large areas of haemorrhage and necrosis occur.

Remarks.—According to the mitotic counts this oesophageal tumour is the most rapidly growing of the "mixed-celled" sarcomas we have encountered. Here again we have a mixture of spindle cells (in this case nearly all more or less modified from the fibroblast type and but little concerned with collagen production) with stellate and amoeboid cells showing cytophagocytic and lipophagocytic functions and at the same time associated with production of reticulum fibrils. These bizarre cells appear to constitute the more rapidly growing part of the tumour tissue. Tumours of the oesophagus may be considered an unusual disease in animals, with the exception of the cat (Gray, 1935) and possibly the fowl.

Diagnosis.—"Mixed-celled" sarcoma (of almost purely histiocytic type) of the oesophagus.

Case 9 (*Fowl*, 5128).

This specimen, which may be more briefly mentioned, consists of portions of the gastro-intestinal tract and liver only. The intestine bears very numerous nodules attached to the serosa and varying in size from a pin-point to 5 cm., often forming diffuse masses by confluence. The gizzard shows, externally, similar growths. The liver appears normal.

Microscopically there are non-encapsulated, neoplastic growths which may almost completely surround the bowel. In a section passing through the duodenal loop, the tumour is seen to unite the two limbs thereof and to invade the pancreas between them. Externally the growth appears to be naked, internally it grows diffusely in the subserous tissue of the bowel and may be limited by the longitudinal muscularis, or the latter may in parts be invaded and destroyed. The inner muscular coat is always intact. The tumour tissue consists in large part of spindle-shaped cells but there is a large admixture of irregular large cells with ill-defined cytoplasmic limits, irregular nuclei with one or two nucleoli which are often extremely prominent: a cell having a n : N ratio of as much as 1 :1·5 was observed. Collagen fibres are poorly developed, but fibrils pervading everywhere between the cells stain for reticulum and the gathering of these into bundles gives a false alveolar appearance. In many places there are degeneration, oedematous changes, and haemorrhage. The gizzard tumours are similar.

Diagnosis.—Multiple transcoelomic implantations in the bowel and gizzard serosa of a "mixed-celled" sarcoma from an unrecorded primary.

Case 10 (*Fowl*, 13051).

The liver is affected by multiple, small, unencapsulated foci of whitish colour, varying from ·5 mm. to 5 mm. in diameter and irregularly rounded in shape. Some have a fairly well defined margin, others show a darker reddish zone at the periphery.

Microscopically, these scattered foci are seen to grow destructively in the liver tissue, infiltrating the parenchyma at their margin, where there is often a " reaction zone " of lymphocytes and plasma cells. This neoplastic tissue consists of cells of very irregular size and shape, dispersed in an intercellular stroma which is partly collagenous but chiefly reticular in nature. The cells vary from spindle-shaped elements resembling fibroblasts to stellate and polygonal elements of bizarre morphology, the latter being in the majority. These cells are characterised by their large size (up to 150μ) and by deeply staining (deep mauve with haemalum-eosin) cytoplasm. The nuclei are most varied in size and shape: oval, elongate, irregularly rounded, kidney-shaped and often quite irregular and bizarre, with lobation and irregular angular outlines. They are of vesicular type. There are one or two nucleoli visible and in most of the cells they are clearly enlarged, and may show a central rarefaction, thus appearing ring-shaped. The n : N ratio is often 1 : 9 to 1 : 12 and reaches 1 : 3; but in the majority of the cells it is about 1 : 20. The largest nucleoli measure *ca.* 8μ, actually one measuring 13μ was recorded. They are sometimés blotchy and of irregular shape— much elongated; sometimes this elongate appearance appears to be caused by the fusion of two nucleoli. The nuclei of the large polygonal elements are usually most eccentrically located. Bi- or tetra-nucleate cells are often seen. The cytoplasm may show a number of small vacuoles or a single large one, staining for fat. These large vacuoles cause considerable distortion of the nuclei by pressure.

Diagnosis.—Haematogenous hepatic metastases of " mixed-celled " sarcoma, in this case almost purely of histiocytic type (primary not recorded).

Discussion of the Pathology and Nature of the so-called " Mixed-celled " Sarcoma in the Bird.

From the observation that in four out of eight cases from which primary tumours were submitted, the ovary was the seat of the primary and that in three further cases transcoelomic implantations to the bowel and mesentery were submitted, we may conclude that in fowls the ovary is the organ most commonly affected. The ovarian tumours usually give rise to peritoneal implantations and in all cases haematogenous metastases may occur (liver, spleen, kidney, musculature, epicardium). Most of the tumours were slowly growing and had a mitotic index of less than 1. In their most rapidly growing portions an index of 3 is exceptional and was recorded in one case only. Three cases of the disease were complicated by leucosis (myeloid type twice and lymphoid type once). The tumours are often very haemorrhagic, causing (by their erosion of blood-vessels) extravasations of blood into the neoplastic tissue. These haemorrhages may be prominent to the naked eye and in the cases of abdominal sarcomatosis often serve as an important differential criterion from carcinomatosis, a disease which has usually a very similar distribution in ovary (or oviduct), mesentery, and bowel serosa. Of further importance in the naked-eye differentiation from carcinomatosis are the haematogenous metastases common in sarcoma and rare in the reproductive-tract carcinomas of the bird.

We have assumed for purposes of description that the so-called " mixed-celled " sarcoma of the bird is composed of a mixture of two neoplastic cells whose prototypes are the fibroblast and the macrophage (histiocyte) respectively. This attitule may be justified by the following considerations:—From the work of Carrel and Ebeling (1922, 1926) and Fischer (1925) we know that the avian macrophage can readily transform into the fibroblast, and the close relation of these two types is further shown by the observation that in the histogenesis of the Rous sarcoma the macrophage or histiocyte plays an important or exclusive part (Haddow, 1933). Further, on general theoretical grounds, the fixed histiocyte is to be considered as a modified fibroblast type, differing from the fibroblast in its tendency to be stellate instead of spindle-shaped, to produce reticulum (or pre-collagenous) fibrils rather than collagen fibrils and in playing an important rôle in the production of phagocytic free elements (free histiocytes, macrophages, polyblasts, clasmatocytes) as well as the free cells which constitute the precursors of the elements of the blood. It is not surprising then that in tumours should be found all transitions between these two types, and the cells actually seen in the neoplastic tissue may be compared with three normal elements of the body: the collagen-producing fibroblast, the reticulum-producing fixed histiocyte, and the phagocytic free histiocyte or macrophage. In the tumour tissue these types are observed respectively as spindle-shaped cells producing collagen and tending to be arranged in bundles, anastomosing stellate cells closely associated with a fibrillar reticulum and already having phagocytic properties, and amoeboid elements characterised by active phagocytosis wherever material to be phagocyted exists: viz. (*a*) in the ovary, where the destruction of the Graafian follicles results in the setting free of yolk in the tissue, in the subserous fat deposits, and in the liver, in all of which regions the invasive growth liberates much lipoid material, the lipophagy reaching proportions where the tumour cells may come (superficially) to resemble fat cells; and (*b*) wherever infiltrating cells are present in the tumour tissue, e.g. following necrosis (which is common) or as a reaction zone at the margin of the advancing neoplastic elements: here opportunity occurs for the neoplastic cells to display their capacity for cytophagocytosis, and granular leucocytes and lymphocytes are commonly to be seen enclosed in cytoplasmic vacuoles and in all stages of digestion from still recognisable and identifiable leucocytes to amorphous acidophilic inclusions. This functional characteristic alone allows one with accuracy to speak of the neoplastic elements as macrophages, a term which denotes those cells which are active in phagocyting large particles, whether of organised or unorganised nature. Besides these features, there are others, including the large size of the cell (up to 150μ), the dense cytoplasm, the conversion into " foamy " cells through lipophagy (cf. the " foam cells " in chronic inflammatory reactions), the pleomorphic and often eccentric nuclei, the tendency to form multinucleate giant cells (corresponding with the non-neoplastic " foreign body giant cell " derived from the macrophage or " epithelioid " cell), and the obviously mobile and amoeboid nature (deduced, of course, from the appearance in fixed tissue sections) which are irresistibly reminiscent of the free histiocyte (macrophage or clasmatocyte). Between the spindle-shaped collagen-producing cells, the stellate reticulum-forming or already phagocytosing cells, and the amoeboid phagocytic cells of these tumours there are of course all transitional grades. And from the circumstance that the orderly process of this differentiation which characterises normal tissue is disturbed and the development of the one function (e.g. phagocytosis) may not be preceded by the loss of another (e.g. the collagen-producing function), we are able to observe large phagocytosing and even amoeboid cells whose cytoplasm still retains the function of producing collagen. This observation is of the greatest importance, allowing one to study the development of collagen in a more advantageous manner than is the case when the non-neoplastic fibroblast (either in embryonic, regenerative, or cultured tissue) is studied. In the typical fibroblast, in other words, the cytoplasm is relatively small in amount and much drawn out, so that it is by no means easy to decide whether the collagen fibrils are deposited in the edge of the cytoplasm or actually between the long, narrow cells. This difficulty has been responsible for a controversy regarding the intracellular or intercellular origin of collagen. In the large tumour cells, however, not only are circumstances more favourable to observe that actually the peripheral portion of the cytoplasm may become transformed into collagen, but—and this is still more convincing—the disturbance in the cell may apparently result in a disorderliness or perhaps a re-arrangement of the cytoplasm whereby the faculty of transforming into collagen no longer remains a prerogative of its peripheral part: in consequence one can observe all stages in the development of collagen within the deep parts of the cytoplasm. Being now unable to escape or separate from the cell into the intercellular tissue, the newly-formed collagen forms rounded intracellular globules instead of fibrils. The phenomenon might be described as an abortive matrix formation—the development of the collagen being both misplaced and mistimed with reference to cell-economy.

The further potentialities of the connective-tissue cell type may be shown on occasion by a myxoid transformation of parts of the neoplastic tissue; and in one case some of the haematogenous metastases laid down chondromucin, and then grew as tumours which histologically corresponded with chondrogenic sarcoma (although not typical of the majority of such tumours); or they were composed of less differentiated " round cells " having much the morphology of the lymphocyte.

From the standpoint of practical diagnosis, it is to be emphasized that the tendency seen in some of these tumours, whereby bundles of spindle-cells alternate with groups of the large macrophage-like cells, is not to be mistaken for an alveolar growth leading to a diagnosis of carcinoma, as happened in some of these cases in the routine examination. Familiarity with the appearance of the neoplastic macrophage and the demonstration of an intercellular reticulum between them will easily allow this mistake to be avoided. Further, especially when only metastatic lesions may be submitted for diagnosis, the bizarre nature of the cells in the spleen and the liver secondaries may be very puzzling to those not familiar with the transformation described, while extreme lipophagy, especially in subserosal implantation secondaries, might easily result in an erroneous diagnosis of lipogenic sarcoma: one must, as Borst (1902) has pointed out, distinguish between an essential tendency of the cell cytoplasm to differentiate fat, and a phagocytosis of pre-existent neighbouring fat globules, although morphologically the final results of these two very different processes may appear very similar.

Regarding the question of nomenclature it is obvious that the term " mixed-cell sarcoma " is expressive of ignorance regarding the nature of the cells. If it is accepted that the admixed cells are of two chief types—the fibroblast and the macrophage—with the transitions between them, then these tumours should fall into line nomenclaturally with the term fibroblastic sarcoma: they would then, in precise nomenclature, be called " fibroblastic and macrophagic " sarcomas; or, better, " fibroblastic and histiocytic " sarcomas, the latter term having the advantage of indicating that the histiocytes may be either fixed cells associated with production of reticulum (fixed histiocytes or reticulum cells) or free phagocytic elements (free histiocytes, macrophages, clasmatocytes, or polyblasts of Maximow). One is, in fact, embarrassed by the variety of terms which have been used to describe these fixed and free cells in histology and pathology; but the term macrophage is at present in favour and is probably the best one to apply in the present state of our knowledge. " Histiocytic " is a word very suitable to denote the one entity of these tumours, since other sarcomas are also termed according to the functional capacity of their cells (fibroplastic, osteogenic, etc.). On account of the length of the term " fibroplastic and histiocytic " it may, on the other hand be convenient to use merely the term histiocytic sarcoma, it being understood that fibroblasts may also be expected to be present, or to retain the term " mixed-celled " as a convenient short designation: provided that its meaning be clearly understood, there can be little objection to it. The main point that I have tried to make is that the pleomorphic nature of the cells of these tumours is not to be interpreted as a mere anaplasia on the part of fibroblastic cells. On the contrary the transformation parallels the differentiation-potentiality of their non-neoplastic prototypes and is in fact the reflection, in neoplasia, of a " purposeful " or economic process in the organism. Anaplastic changes (nuclear and nucleolar distortions, etc.) it is true are more in evidence in the neoplastic macrophages than in the neoplastic fibroblasts, but such changes are to be distinguished so far as possible from the distortions of shape resulting from excessive phagocytosis and from the pleomorphism which is characteristic of the non-neoplastic macrophage as well; that the true anaplastic changes mentioned are more evident in the macrophages than in the fibroblasts is apparently referable to the fact that the former cell type tends to constitute the more actively growing (" malignant ") parts of the tumour, as is seen by its frequent predominance at the growing edges of the tumours and in the metastases.

4. *Myxogenic Sarcoma* (Myxosarcoma).

The collection contains two examples of this tumour, one affecting the paranasal sinuses of a bovine (11648) (see Fig. 129) and one situated in the ovary of a fowl, and producing implantations on the serosae. It may be remarked that not a little difficulty was experienced in separating myxoma and myxogenic sarcoma, especially in the bird. Tumours described as myxomata are usually relatively acellular; yet in our collection all gradations of cellularity exist, and what is surprising is that these degrees of cellularity are not necessarily reflected by the mitotic counts; e.g. mitoses may be present in a relatively acellular myxoma, and in densely cellular tumours mitoses may be impossible to find. The degree of cellularity of course depends on the quantity of the mucinous matrix, but this apparently is not an infallible criterion of the rate of growth. A not dissimilar problem has been mentioned under the heading of lipogenic sarcoma, where it was seen that cellularity and incomplete fatty differentiation do not necessarily denote a malignant tumour (lipogenic sarcoma). The problem of discriminating myxoma and

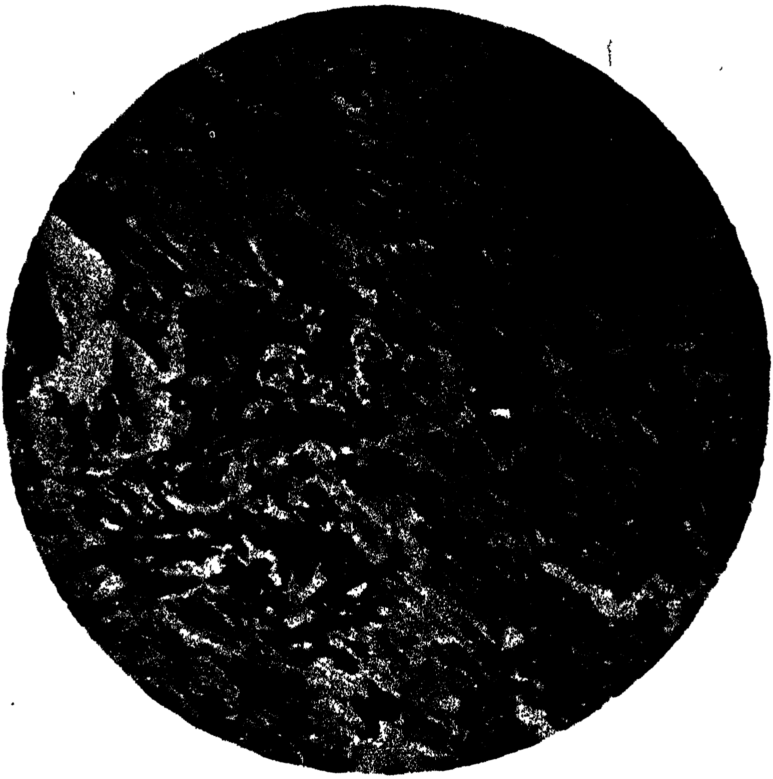

Fig. 129.—Structure of myxoplastic sarcoma of the paranasal sinuses of an ox. (11648; 240×).

myxogenic sarcoma is made none the easier by the fact that (in the bird) the myxoma may lack a specialised capsule and that neither tumour is likely to give rise to true (haematogenous) metastases. One has to rely, in the last resort, on the demonstration of actual infiltrative growth in the case of myxogenic sarcoma, rather than on the histology and cytology. Typical cases are, of course, easily distinguished.

5. *Chondrogenic Sarcoma* (Chondrosarcoma).

This tumour is not represented in the Onderstepoort collection. It will be remembered however that in one case in the fowl (15100) subepicardial metastases of mixed-celled sarcoma grew as chondrogenic sarcoma.

6. *Osteogenic Sarcoma* (Osteosarcoma).

This disease was encountered only in the domestic carnivores, affecting the humerus of a dog (12754)—see Fig. 130—and the hock of a cat (14067).

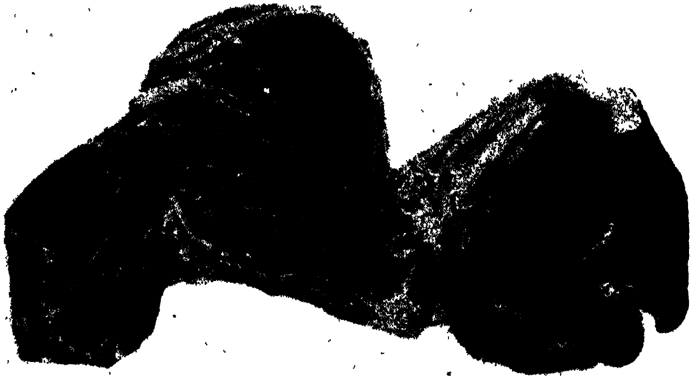

Fig. 130.—Osteogenic sarcoma of the humerus of a dog. (12754; 1/3×).

CHAPTER VIII.

Tumours of Endothelium: Angiogenous Neoplasms—Angioma and Endothelioma.

NOMENCLATURE.

THERE is perhaps no group of tumours in which the terminology has been more loosely applied and whose scope has been so variously interpreted as those characterised by the presence of endothelial cells. It is unnecessary to trace here the variations which the conception of the term endothelioma has undergone from time to time and in the hands of different authors. The advisability of excluding, as is done in this work, the mesotheliomas from this group of tumours has been discussed in Chapter VI. Regarding the benign tumours ot endothelium in animals, the older literature contains many reports of the condition, so very frequent in bovines, which we now regard as a multiple telangiectasia of the liver, not a true neoplasm. These lesions will also not be discussed here. Similarly, enlargements of pre-existing lymph-vessels may be confused for true tumours and in fowls we have encountered fairly often cases of multiple cystic lymphangiectasia of the serosae which are likewise to be distinguished from true neoplasms.

Many terms at present in use to describe the members of this group of tumours are most unsatisfactory, either on account of their construction or because they are used without precise definition. The name " angioendothelioma " (like " fibrosarcoma ", " adenocarcinoma ", etc., etc.), is suggestive of a mixed neoplasm and is further undesirable because there is no general agreement as to whether by the prefix " angio-" is denoted that the tumour in question is of angiogenous origin or merely whether it grows angioplastically. One searches many individual works in vain for a clear statement by the authors regarding their meaning in this connection and although Borst definitely states that by the prefix " angio-" is denoted a vascular *origin*, it is almost universal in the English literature to find that the term is used in a purely histological or descriptive sense. In practice such distinction often has little importance, for the reason that most angiogenous tumours reflect their origin in their capacity for angioplasia and it is doubtless this circumstance which leads to lack of clarity in the use of the term " angioendothelioma ". Yet solid or chiefly solid endotheliomas occur which are apparently of angiogenous origin and to separate such from the " angioendotheliomas " which differ only in the degree of differentiation is highly misleading.

An approach to an ideal classification of the group of tumours characterised by the presence of endothelial cells as an essential part of the neoplastic tissue seems to me to be the following:—

- A. Angiogenous neoplasms:—
  - (1) Angioma(¹) (benign).
  - (2) (Angiogenous) endothelioma:
    - (*a*) Angioplastic(²).
    - (*b*) Solid.
    - (*c*) Mixed, i.e. *partim angioplasticum*(²) *et partim solidum*.
- B. Non-angiogenous neoplasms:—
  - (1) Dural endothelioma(³).
  - (2) Coelomic "endothelioma" (better classed separately as mesothelioma).

Angioma.

1. Haemangioma.

Only two cases of haemangiomata were encountered. Feldman's (1932) review of the endothelioblastomas indicates sufficiently the relative frequency in the dog of angiomas on the surface of the body. Both our cases affected the skin of dogs, the lesions being situated in the tibial (Canine, 15102) and hip (Canine, 12062) regions respectively. The literature contains no reports of haemangioma in other domesticated species, and my own experience bears this out. Other lesions previously diagnosed as haemangiomata are not included here. They comprise many cases of capillary telangiectasia of the liver of bovines, which are no longer considered as neoplasms; a case of venous varicosity and thrombosis affecting the oviducal ligament of a fowl (7192) which had been diagnosed as a cavernous haemangioma but which I did not consider to represent a neoplasm; and cases which on re-examination were considered to be angioplastic endotheliomata, which will be described under that heading.

2. Lymphangioma.

Four satisfactory examples of this uncommon lesion have been encountered. [Dr. A. D. Thomas of this Institute has, in an unpublished work, recorded multiple tumours(?) of the skin of bovines, appearing in a herd on an apparently hereditary basis (congenital lymphangiomata?) The lesions were characterised by copious "weeping" of a lymph-like fluid, but the material obtained (under conditions of difficulty) at biopsy for histological study was inadequate and the clinical diagnosis could not be confirmed with any certainty.]

(¹) To this term the qualification "haem"—or "lymph"—may be prefixed to indicate that blood- or lymph-vessels respectively are referred to; further it is usual to indicate by one of the qualifying terms "*simplex*", "*cavernosum*", or "*cysticum*" whether the lumina which are formed are of capillary, venular, or still larger (dilated) dimensions respectively.

(²) Here again "haem"—or "lymph"—is prefixed.

(³) The existence of this neoplasm as a non-angiogenous tumour is doubtful.

Such tumours are well known to be very rare. Feldman encountered none in his material, and he does not comment on the morphological features of these growths in domestic animals. Some cases are recorded in the literature in horses, by Bernadini (1906 and 1909), by Nocard, cit. Folger (1917), and by Markus (1903); in the dog one case was described by Hieronymi and one by Medwedew (1910). All were subcutaneous in position except the case of Markus, in which the pleura and pericardium of a horse were affected.

In view of the rarity of these tumours it is interesting that at least four cases have occurred in South Africa. In neither the mule nor the ox, in which species (in addition to the horse) these lesions are here reported, could reports of lymphangioma be traced in the literature.

Case 1 [*Equine* (*Mule*), 15537].

This specimen consists of a globular tumour, measuring *ca.* 10 inches in diameter, removed from the flank of a twelve-year-old mule. It was reported to have been gradually enlarging over a period of 7 years. It consists of a number of larger and smaller cystic cavities filled with whitish fluid.

Microscopically, thicker and thinner branching septa of collagenous tissue carrying blood-vessels are arranged to enclose larger (3 to 4 mm.) and smaller (150μ) cavities filled with lymph and lined by endothelial cells showing no morphological departures from the normal cytology of such elements. Occasional erythrocytes occur in the contained lymph. The whole mass is well circumscribed and thinly encapsulated.

Diagnosis.—Lymphangioma cavernosum.

Case 2 (*Bovine*, 12040).

In this case the cite was not stated. The microscopic findings were identical with the above.

Diagnosis.—Lymphangioma cavernosum.

Case 3 (*Equine*, 8045).

The specimen consists of a flattened, oval growth smoothly covered by serosa and broadly attached to the costal pleura of a horse in which no other neoplasm was found at autopsy; the primary nature of the lesion is therefore well attested. It measures 2·5 cm. in diameter and is raised ·5 cm. above the surrounding pleural surface.

Microscopically (Figs. 131 and 132), a well-developed collagenous stroma demarcates irregularly rounded or polygonal lobules or streak-like tracts which lie irregularly dispersed in the connective tissue of the thickened subserosa of the pleura. The parenchyma is composed of flattened cells which are closely associated with reticulum fibrils and also with a very variable amount of collagenous tissue. In most of the lobules these cells are clearly arranged as a lining to lumina which are filled with lymph, but the degree of lumen formation varies greatly in different lobules and even in

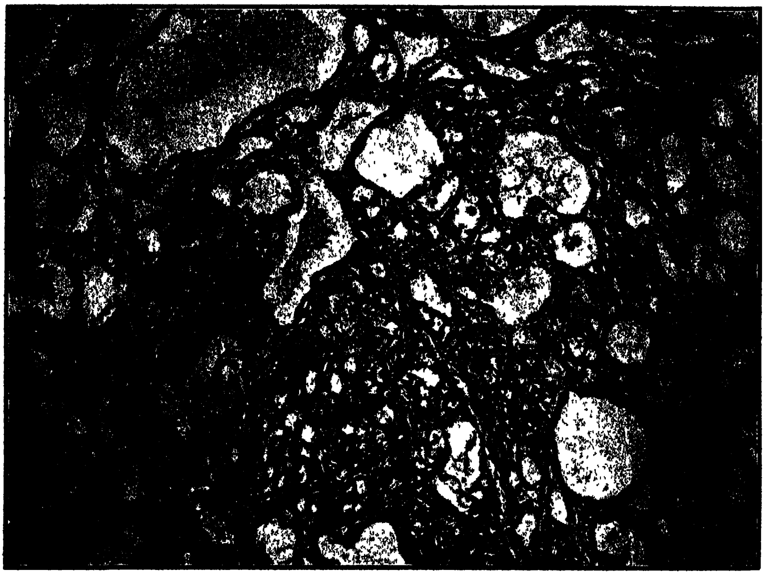

FIG. 131.—Lymphangioma of the costal pleura of the horse: Capillary and, predominantly, cavernous types of growth. (8045; 110×).

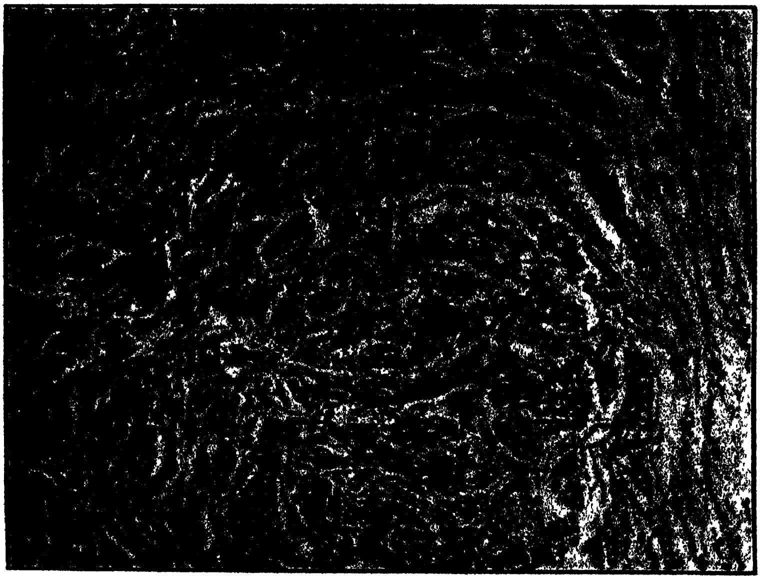

FIG. 132.—Another part of the lymphangioma shown in fig. 131: Lumina less well developed, giving a partly solid and partly capillary type of growth. (8045; 110×).

different parts of one and the same lobule. Thus all transitions can be traced between (*a*) solid sprouting strands of cells which appear often to be burrowing their way into the adjacent stroma (Fig. 132), (*b*) the formation of many closely set lumina of capillary dimensions (e.g. 7 to 10μ) (Fig. 132), and (*c*) areas where much larger lumina predominate (Fig. 131) and which are associated with a greater amount of collagen formation and a lesser degree of prominence of the endothelial-like lining elements. The cells, which may measure some 20μ in diameter, have oval, amblychromatic nuclei which are larger and less regular in outline in the parts where lumen-formation is more rudimentary: in such parts also the nucleoli reach larger dimensions (e.g. n : N = 1 : 16) than in the less active portions of the tissue, where the nucleoli are comparatively inconspicuous (e.g. n : N = 1 : 25) although larger than those of normal endothelial cells and distinctly acidophilic. The neoplastic tissue is covered superficially by a thickened subserosa which contains many somewhat dilated lymph-vessels not apparently of neoplastic nature, but often difficult to distinguish from the more outlying vascular units of the neoplastic islands: the apparances are consistent with the derivation of the tumour from the lymphatics of the pleura and no continuity can be traced to the unbroken and non-mobilised mesothelium.

Remarks.—This neoplasm, while clearly of angiogenous nature, might occasion difficulty in deciding whether the term angioma should be applied to it or whether it should rather be regarded as the lymphangiogenous counterpart of the haemangioplastic and partly solid haemangiogenous endotheliomas to be discussed (cf. especially the porcine case—Case 1). The degree of cellular anaplasia (including the somewhat enlarged nucleoli) in parts might indeed be held to warrant a diagnosis of endothelioma; but in the absence of mitosis and of a clearly invasive growth-tendency the tumour is better termed an angioma. Although areas of " solid " growth are prominent, it is apparent that these parts represent budding neoplastic capillaries which are destined soon to acquire lumina and that the usual criterion used in distinguishing endothelioma from angioma, viz. predominance of cellular proliferation over angioplasia cannot be said to operate in this case. The principles of this differential diagnosis are dealt with at greater length in the discussion of the endotheliomas. Lymphangioma of serous membranes is to be considered as a rare neoplasm of domestic animals; a case has already been reported by Markus (1904), the subject also having been a horse. One should here recall the discussion on the classification of tumours of the serous membranes in Chapter VI, where was pointed out the necessity of avoiding the use of the term " endothelioma " whereby to designate neoplasms of mesotheliogenous origin. By calling such tumours mesotheliomas one is able clearly to distinguish them from neoplasms such as the one we are now dealing with, which although also primary in the serosae have nevertheless an entirely distinct histogenesis, viz. from vascular endothelium, and to which the term angioma or endothelioma may therefore be fittingly applied.

Diagnosis.—Lymphangioma (*partim simplex et partim cavernosum*) of the pleura.

10

Case 4 (*Bovine*, 3589).

The specimen (see Fig. 133) consists of very numerous tumours situated on the thoracic surface of the diaphragm. They vary from single, pinhead or pinpoint sized, scarcely visible, solid, greyish, flattened nodules, of irregularly circular to elongate-oval outline, to larger aggregations (up to 6 cm. across) composed of both solid nodules and pedunculated, transparent, thin-walled cysts measuring some 1·5 cm. in diameter; solid nodules and cysts are intimately intermingled in these large plaques, and they are flattened by pressure and their circumferences separated by deep clefts. Apart from the cyst-formation, these lesions bear a distinct resemblance to those of case 7 (to be described). The smallest solitary nodules are raised 1 to 2 mm. above the surrounding surface, the somewhat larger ovoid ones up to ·5 cm. There are also a few isolated, larger, solid nodules measuring as much as 1·5 cm. in diameter and raised ·75 cm. above the surface. All the lesions are smoothly covered by the serosa.

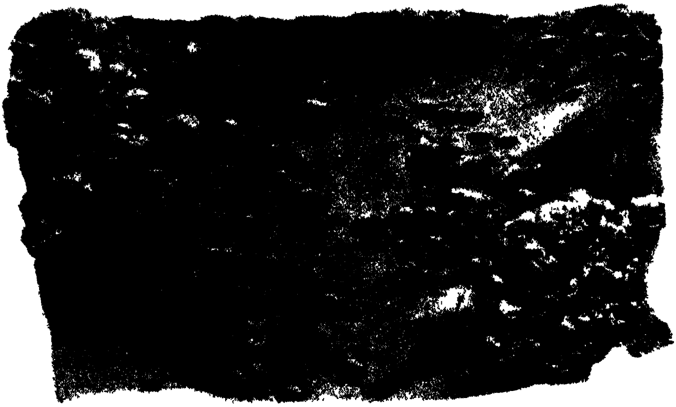

FIG. 133.—Multiple simple and cystic lymphangioma of the diaphragmatic pleura of the ox. (3589; 2/5×).

Microscopically, the solid lesions are composed of long, thin, parallel strands of cells having the morphology of endothelials and intimately related to the connective-tissue fibrils which intervene between the adjacent strands. These strands are often two cells in width and are partly solid and in other parts excavated to enclose small lumina of capillary dimensions. Or lumen formation may be more prominent, and lymph-containing cavities varying from 7μ to 40μ in diameter are lined by more flattened or by plumper cells of the same type. There are all transitions through nodules composed largely of cavernous endothelial-lined spaces to the large cystic lesions described macroscopically. In the solid parts collagenous tissue preponderates over the cell strands which it separates, in the cavernous parts thin collagenous septa lined by the flattened neoplastic cells separate the lymph-containing lumina. No mitoses were seen, and the nucleoli are minute (1 : 25 to 1 : 50). There is no continuity of the tumour tissue with the overlying, intact mesothelium.

Remarks.—The lymphangiogenous origin of these multiple lesions is obvious from their histology and cytology. The only difficulty arising in diagnosis is whether the neoplasm is more appropriately to be termed lymphangioma or lymphangiogenous endothelioma. In favour of the former are the absence of mitoses and the lack of nucleolar enlargement. And although in these tumours there might be thought to be a preponderance of cell-multiplication over lumen-formation, no invasive growth is demonstrable and the multiplicity is obviously a primary one.

Diagnosis.—Multiple lymphangioma (*partim simplex, partim cavernosum, et partim cysticum*) of the diaphragmatic pleura.

Angiogenous Endothelioma.

All endotheliomata encountered in this country have been of angiogenous origin. Dural endotheliomas have not been encountered and are possibly the rarest of tumours of the domesticated animals, only one case described under that name being recorded in the literature (Stadler, 1915). [Two cases of " psammona " are also quoted by Joest. In neither of these, however, was an endothelial origin considered. In man, meningeal " psammonas " are considered to represent hyalin-degenerated and calcified endotheliomas (Ewing), but the position with regard to meningeal " sarcomas " in both man and animals is very obscure]. It is of course by no means certain which dural endotheliomas may not be angiogenous in origin; i.e. it is not certain that any of these neoplasms actually arise from the meningeal endothelia (as urged by Engert, 1900); and it is possible that, on the other hand, they arise from lymphatic endothelium, or even, in certain cases, from rests of embryonic vasoformative cells (Albrecht, 1902). Peritoneal, pericardial, and pleural " endotheliomas " arising from the coelomic lining cells have in this study been classed separately as mesotheliomas. And it is possible that dural endotheliomas which can be shown to have arisen from the lining cells of the dura should be classed with them; for Maximow (1930) is of opinion that these elements represent a mesothelium homologous with the lining cells of the coelom.

From the angiomas, composed of neoplastic blood-vessels, must be distinguished (malignant) tumours of endothelial cells considered to arise from the lining cells of vessels. When these are highly angioplastic, much the same judgment is to be used in distinguishing them from the (benign) angiomas as has to be used to discriminate, e.g. fibroma from highly fibroplastic sarcoma (" fibrosarcoma "). In other words, my plea is that this terminology should fall into line with that in use for the connective-tissue or epithelial neoplasms, to give us benign tumours—angioma, fibroma (or e.g. osteoma) and adenoma; contrasted with malignant tumours of the same general appearance, viz. angioplastic endothelioma, fibroplastic (or e.g. osteogenic) sarcoma, and adenoid carcinoma. One objects as much to the use of the term " malignant angioma " as to " malignant adenoma " or " malignant fibroma ". The last term is, fortunately, not used but it is no more unsuitable or confusing than the two former.

In considering the endotheliomas in the collection it is very difficult, if not impossible, to carry out a rigid separation between those that are solid and those that are angioplastic. Most grow in both fashions; where one type of growth clearly predominates, I have used the terms angioplastic or solid as the case may be. Several may be classed as partly angioplastic and partly solid, and by this is not meant merely that portions of the tissue are more compact while in others lumina are more easily recognisable: for in the growth of endothelial cells, whether neoplastic or non-neoplastic, it is well known that lumen-formation occurs secondarily in sprouts which at first are solid; for this reason, one may expect to find in the more rapidly growing portions of an endothelioma, neoplastic cells which, although growing in solid formation, are later destined to angioplasia. The term " solid " is, strictly speaking, to be applied only to those tissues where the compact form is considered to be a permanent growth mode, not a temporary condition depending on the youth of the newly-formed tissue.

Our cases of angiogenous endotheliomas are eight in number and they are found to fall into the two categories " *angioplasticum* " and " *partim solidum et partim angioplasticum* ". No purely solid tumours were encountered, but in five cases the solid parts greatly predominated over the vessel-forming parts of the tissue; and in one of these it was not until a number of sections had been cut that portions were encountered showing a tendency to angioplasia. Both of the purely angioplastic tumours were of the haemangioplastic variety. Of the six mixed types, two were considered partly solid and partly haemangioplastic, one was predominantly haemangioplastic with solid areas, and the other three partly solid and partly lymphangioplastic. The histological gradation from a high degree of angioplasia to solid tissue which over large areas completely lacks signs of angioplasia, leads one to believe it likely that angiogenous tumours of domestic animals might be encountered which are purely solid in type. As Piney (1926) has remarked, " not all parts of every haemangioma show the development of obviously vascular channels; some areas may be composed of compact masses of cells ". And Fraser (1920) urges " that the classification of ' haemangiomata ' should depend on the variety of histological structure, and more especially on the density of its structure "; he has described (in man) compact (solid) varieties of endothelioma which result according to him from the endothelial cells lining the units of the angioplastic (capillary) type of tumour taking on " active proliferation ". To put it shortly, angiogenous origin might not always be reflected in angioplasia; and in some of our tumours signs of angioplasia have been hard to detect. Piney indicates further that the degree of angioplasia is not a measure of the benign nature of the tumour and with this we are to some extent in agreement: circumscribed and encapsulated tumours on occasion may be found to be very compact, while infiltrating tumours may be more angioplastic. This need not surprise us, because we are already familiar with the danger of estimating the degree of malignancy of a tumour by any single criterion. We know well, for example, that sarcomas with a prominent tendency to fibroplasia may sometimes prove more malignant than more cellular tumours, that even fibromas may sometimes be very cellular, that to attempt a distinction between myxoma and myxogenic sarcoma purely on the basis of the abundance of the mucinous matrix would often lead one into error; that indeed neither the signs of function on the part of tumour cells nor anaplasia of those cells are certain measures of the clinical behaviour of tumours, but only that it is more usual for a high degree of cellular differentiation to be the accompaniment of more benign, and a high degree of cellular anaplasia to be that of more malignant processes. In the last analysis both histological and cytological criteria of malignancy may fail, the search for a specific morphological criterion of the "malignant" cell or of the "malignant" tissue having proved inconclusive, although it has been most fruitful in aiding our judgment.

Endotheliomas were encountered as follows:—Affecting the skin or subcutis—three cases in the dog, the pig, and the mule respectively; affecting the heart—two cases, both in bovines; affecting the liver and spleen—one case, in the sheep; affecting the pleura—one case, in the horse; and affecting the ovary—one case, in the mule.* On account of the interest attaching to these tumours and the difficulties of diagnosis, they will be described here in detail. In only 3 of the 11 cases was a lymphangiogenous origin considered probable.

(a) HAEMANGIOGENOUS ENDOTHELIOMATA.

Case 1 (*Porcine*, 14967).

The subject was a Tamworth boar, five years of age, which appeared to be (apart from the tumours) in good health and in fairly good condition, and from the scrotum of which biopsy specimens were removed for diagnosis. It was reported that multiple tumours on the skin of the scrotum were so numerous that the whole surface was "one mass of them"; a few isolated tumours were present on the hind legs in the hock region and a few on the rump. The length of time over which the condition developed was stated to have been more than a year. The tumours were seen (by the attendant) to commence "in the form of scaly pimples", and to increase slowly in size up to that of the larger of the growths submitted. While the animal was under veterinary observation this new development of tumours was also seen. The tumours were freely movable, with the skin, over the underlying tissues (4).

The specimen consists of two "wart-like growths". The smaller one is an oval papule covered by hairless epidermis, to which it is intimately attached and which over a considerable part is deficient (ulceration), measuring 1 × ·5 cm. and raised ·5 cm. above the surrounding surface. On section a prominent and close connective-tissue meshwork is seen enclosing a softer greyish tissue as small alveoli *ca.* 1 mm. in diameter. The larger is a rounded, warty growth measuring 1·5 × 1 cm. and raised 1 cm. above the surrounding surface. It is broadly pedunculated and situated beneath the epidermis, which, however, is over the greater part deficient, showing a shallow area of ulceration covered with reddish-brown crusts. On section, a connective-tissue stroma is less prominent, the softer greyish tissue is present in larger amounts and in parts this has a red discolouration.

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* This case is reserved for a subsequent communication.

(4) I am indebted to the Government Veterinary Officer, Potchefstroom, for his kindness in supplying these particulars.

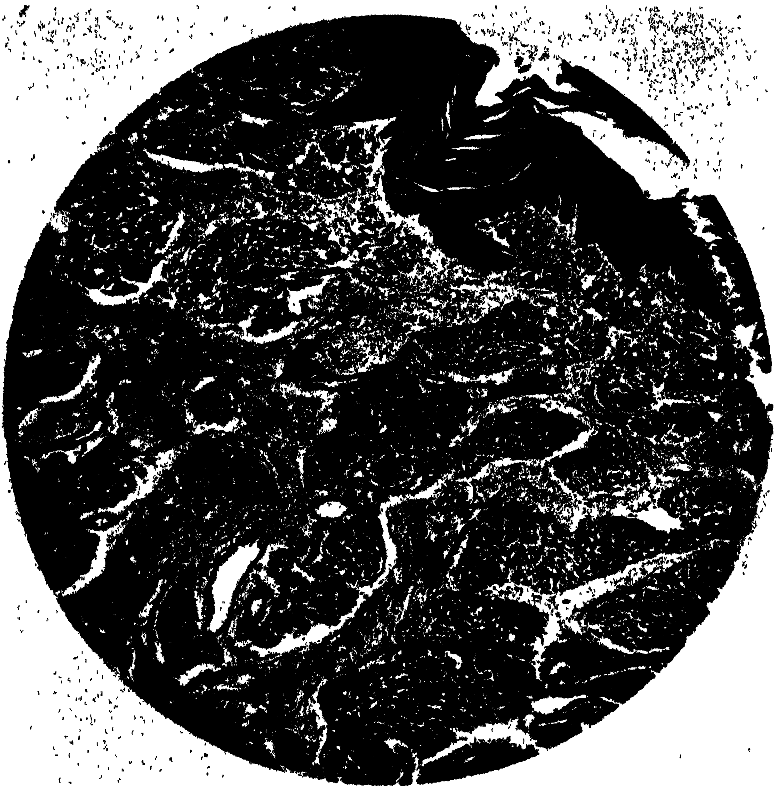

FIG. 134.—Haemangioplastic endothelioma of the skin of the pig: Invasion of the derma by neoplastic endothelial cells arranged for the most part to line capillary lumina. (14967; 60 ×).

Microscopically (Figs. 134 and 135), the smaller growth is limited to the *cutis vera* and is not encapsulated. It consists of a stroma of collagenous tissue which is well supplied by non-neoplastic blood-vessels and which supports, at rather widely separated intervals, anastomosing strands of parenchyma consisting of agglomerations of blood-filled neoplastic capillaries and, occasionally, slightly wider vessels of the same nature. Under low power, this tissue presents a characteristic spongy appearance and a " curled " arrangement of the cellular elements. The cells are arranged for the most part as a single lining layer to the blood-channels, backed by delicate connective tissue: they are flattened in shape, have palely-stained nuclei, and inconspicuous nucleoli (n : N = 1 : 50) which do not give an acidophilic reaction; they do not differ in morphology from endothelial cells of normal capillaries except that they are slightly more prominent. But there are other areas (and these portions are very similar to the " haemangioendothelioma " of the skin of a pig illustrated on p. 500 of Joest, *Bd.* III) where there is a tendency for the vessels to be lined by more than one layer of cells. In these parts an appearance which is familiar throughout the endotheliomas is seen, viz. that it becomes impossible to distinguish a boundary between the typical neoplastic endothelial cells and surrounding fibroblasts of the " stroma ", because (apparently) the endothelial elements become associated with the development of fibrils. Further,

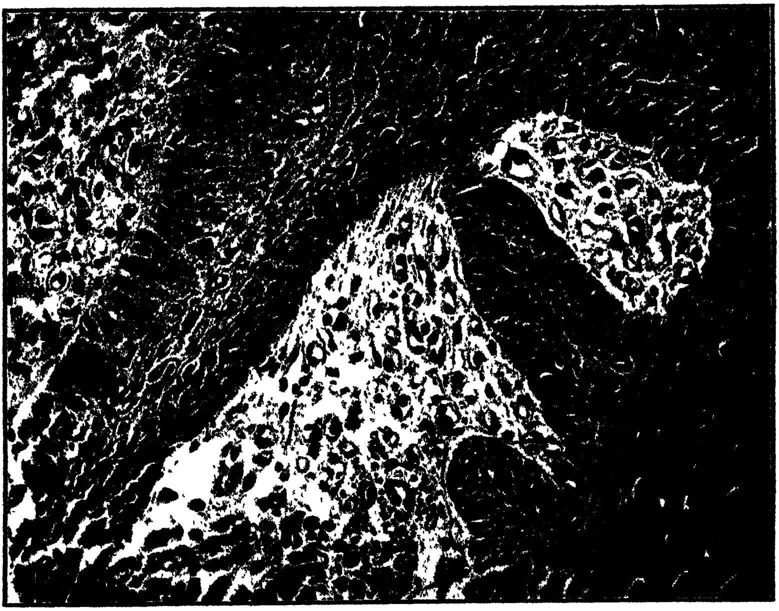

FIG. 135.—Less anaplastic portion of the endothelioma of the pig shown in fig. 134: Infiltration of the dermal papillae by neoplastic capillaries whose growth at this point is resisted by the epidermis. (14967; 250 ×).

these ambiguous cells have more prominent nucleoli (n : N = 1 : 25) which now are distinctly acidophilic. Nowhere, however, is the tendency to blood-vessel formation completely lost. The neoplastic tissue follows the dermal papillae upwards and is usually separated from the epidermis by a thin zone of uninvaded, loose collagenous bundles of the *cutis vera*. But in many parts the neoplastic endothelial cells are separated from the *stratum germinativum* only by the thin connective-tissue backing which binds them into blood-vessels (Fig. 135). In the region of ulceration there is haemorrhage and a rich infiltration of neutrophils which are also prominent within the neoplastic capillaries. The surface is covered by a crust of cellular debris with a rich bacterial flora. Mitoses are absent.

The larger tumour (Fig. 136) is very similar to the smaller in respect of its topography, viz. it occupies the *cutis vera* and is unencapsulated. There are several morphological grades of the neoplastic tissue:—(*a*) Limited areas have the structure which characterises the greater part of the smaller tumour (i.e. the structure ot capillary haemangioma). (*b*) A larger amount of this tumour corresponds to those parts of the smaller tumour characterised by cellular proliferation rather than vascular growth, although the tendency to vessel-formation is still predominant. (*c*) A single area, demarcated by the stroma, is seen in which the vascular spaces are considerably larger and where there is considerable crowding and a tendency to layering of the lining cells. Here the connective-tissue backing to the vessels is broader than usual. Many of the cells show conspicuous acidophilic nucleoli.

In these three types of tissue, no mitotic figures are seen and the cells are relatively uniform excepting as regards the finest details of nuclear structure; further the supporting connective tissue is arranged in trabeculae which are much thinner and on the whole more cellular and looser in texture than in the smaller tumour, but which have well-differentiated collagenous fibres.

(*b*) In considerable portions of this tumour, especially in its deeper parts, there is a very definite preponderance of cellular proliferation over vessel-formation (Fig. 136). Although lumina are always to be found, in many cases they seem to be completely obliterated by cellular proliferation; and the endothelial cells, which are now frankly anaplastic, showing considerable variation in nuclear size and often with large acidophil nucleoli (which are frequently double) grow almost diffusely. The n : N ratio reaches 1 : 14, indicating a very definite enlargement for endothelial nucleoli. The cells may be arranged in small groups having a faintly concentric tendency (whorls) or in double rows, separated by a collagen-forming tissue which is now minimal in amount. In these areas mitoses are frequent and the coarse connective-tissue trabeculae have been pushed widely apart by the pressure of the growth, so that a much more highly cellular appearance results. Here and there large lakes of blood are seen which appear not so much as haemorrhages, but as the contents of neoplastic blood-spaces whose walls are more dilated and less well defined.

Over a large part of the surface the epidermis is deficient and here there is an exudate of cellular debris, red-blood-corpuscles and haematogenous pigment, and an infiltration of neutrophils.

Remarks.—The smaller tumour has largely the structure of capillary haemangioma (plexiform angioma); but the presence of portions which show a tendency for cellular proliferation to be more prominent than lumen-formation leads one already in this case to suspect that one is not dealing with haemangioma, although no mitoses are seen and the growth is well circumscribed. The larger tumour presents much more definite signs of "malignancy": areas in which cell proliferation preponderates over lumen formation are so predominant that actual solid areas occur, with numerous mitotic figures and a comparatively advanced degree of cellular anaplasia;

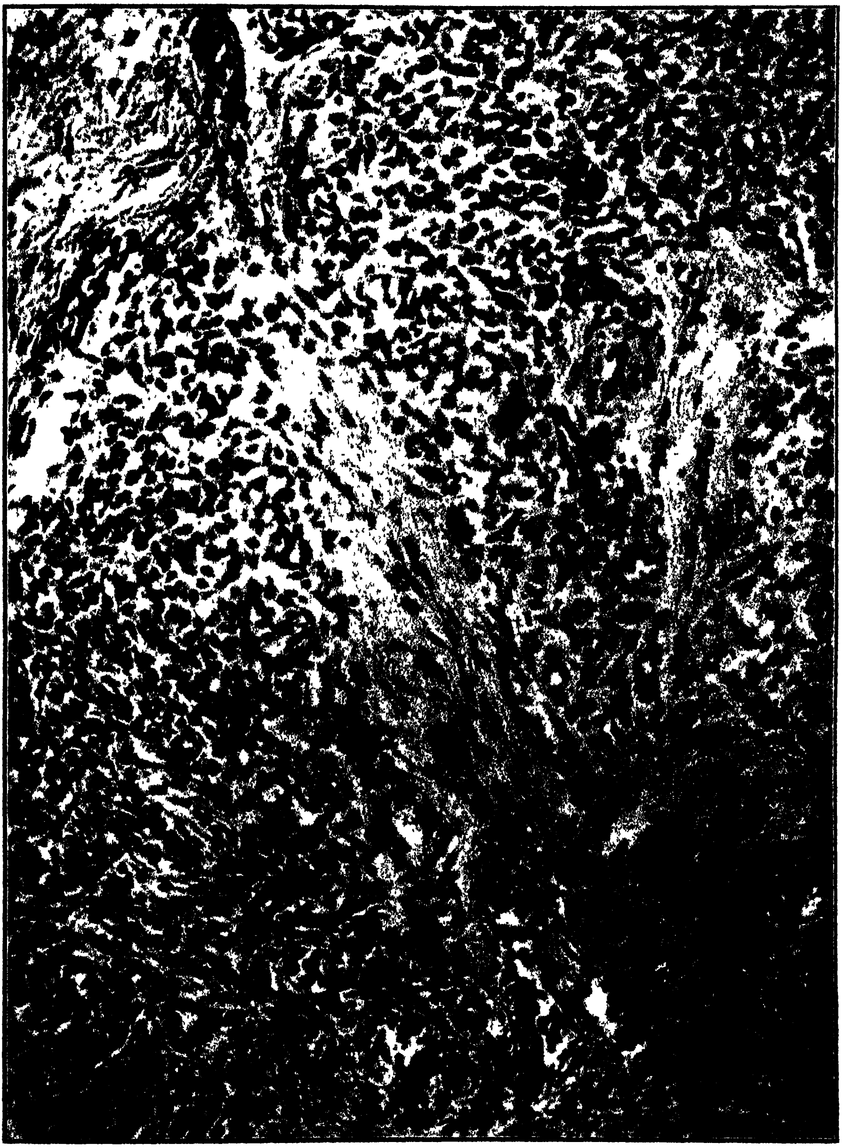

FIG. 136.—More anaplastic type of growth in angiogenous endothelioma of the pig (same subject as figs. 134 and 135). Lumen-formation very rudimentary; the lesion is ulcerating through the epidermis and is infiltrated with leucocytes. (14967; 240 ×).

here the increase of nucleolar-nuclear ratio, already seen in its inception in parts of the smaller tumour, becomes quite striking. This neoplasm has already acquired a locally destructive and invasive growth.

Diagnosis.—Multiple haemangioplastic endothelioma of the skin.

Case 2 (*Bovine*, 5144).

The specimen consists of the heart of an ox slaughtered at the Pretoria Abattoirs. Macroscopically (⁵) there is a large, irregularly oval enlargement situated on the caudal aspect of the heart above the coronary groove and occupying the wall of the left atrium (Fig. 137). It measures *ca.* 11 × 8 cm. Externally it is for the most part covered by the thickened epicardium, but defects occur in this serous membrane. Deeply it infiltrates the myocardium extensively. Internally it is covered by the endocardium but in one place (immediately dorsal to the caudal cusp of the mitral valve) it forms a fungating, fissured protruberance into the atrioventricular orifice, about 3 cm. in diameter. The consistence is firm, but less so than that of the myocardium. Connective-tissue septa, rich in

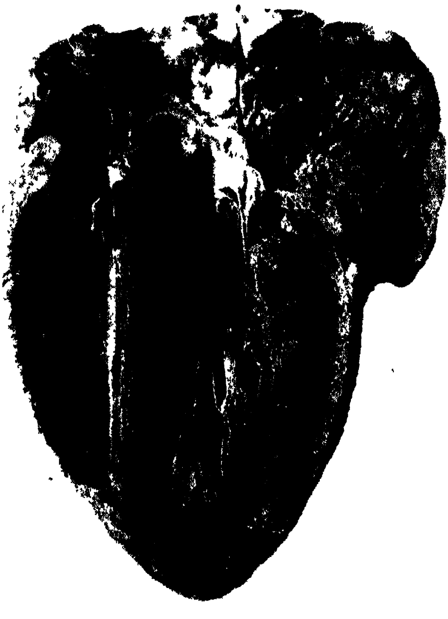

FIG. 137.—Haemangiogenous endothelioma of the myocardium in a bovine. (5144; 1/3 ×)

(⁵) In this macroscopic description, use is made of certain observations on the fresh specimen by Dr. P. J. Fourie.

blood-vessels, course through the growth, and in parts blood-vessels may be closely packed, giving a somewhat spongy appearance. The colour is greyish white, but dark red areas occur. There is a central cavity 2 cm. in diameter having roughened walls and containing bands of fibrous tissue and strands of fibrin. The more dorsal part of the tumour shows opaque (necrotic) areas. Owing to the great thickening of the atrial wall caused by the presence of the tumour, the lumen of this cavity is considerably diminished; but there is a greater tendency for the enlargement to be directed outwards, so that a projection of nearly 2 cm. beyond the coronary groove occurs. The external surface is irregularly fissured and somewhat bossellated. The neighbouring epicardium of the ventricle and also that elsewhere on the ventricles and atria is roughened by a deposit of fibrinous shreds and tags which in parts has a dark reddish brown colour (from admixed blood).

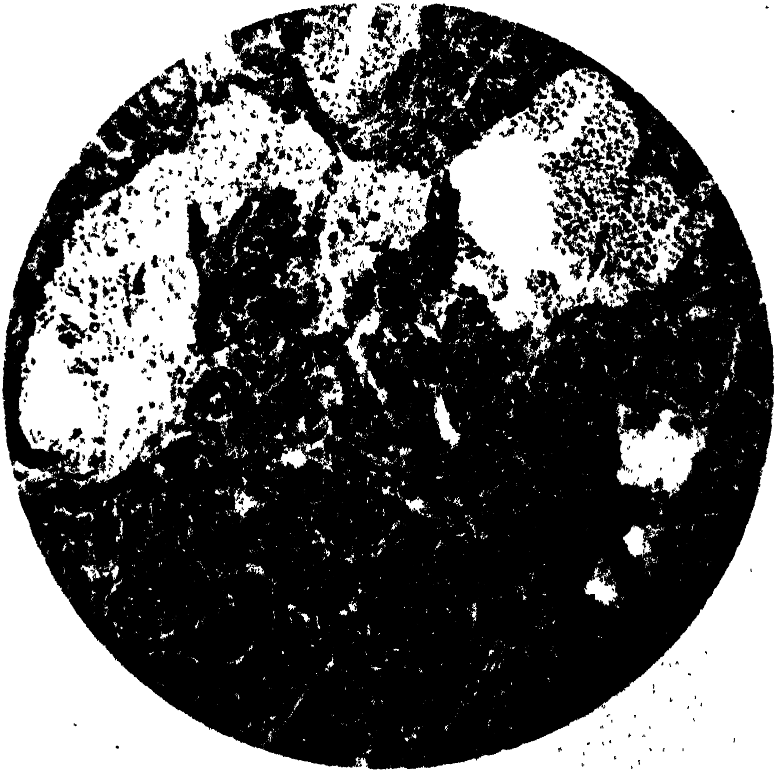

FIG. 137A.—Structure of endothelioma of the bovine heart (fig. 136): Solid and angioplastic types of growth. (5144; 240 ×).

Microscopically (Fig. 137A), the neoplastic tissue has a prominent branching "stroma" composed of bands of collagenous tissue reaching a breadth of several millimetres, but which are much more delicate in what prove to be the younger and more active parts. The character of this stroma varies in respect of differentiation, some bands being acellular and consisting of dense bundles of collagen fibres, and others cellular, having a rich content of fibroblasts: the latter trabeculae may become continuous with actual fields where such tissue predominates in the picture and which are virtually granulation tissue with active fibroblastic proliferation, budding of capillaries, and an infiltrate of round cells, erythrocytes, and macrophages. In places these fibroblasts have a peculiarly loose distribution and are growing into masses of fibrin. Here also plasma cells are fairly frequent and have a predilection for the edges of the stroma, abutting on the parenchyma. In the thick septa occur dense condensations of collagen, some of which resemble osteoid tissue, being hyaline, staining intensely with acid fuchsin and containing lacunar spaces (with radiating canaliculi) in which occur shrunken cells. In such parts the parenchyma occurs merely as scattered islets, often encircling stromal blood-vessels and producing a (false) peritheliomatous appearance; and there occur also large foci of round cells undergoing extensive necrosis. The large septa contain blood-vessels with large lumina and thick walls, and in them wide lymph-containing vessels are also seen. Into the latter invasive growth of the neoplastic cells may occur From the main trabeculae, which in other parts of the growth are far less prominent and more differentiated than has just been described, proceeds a rich system of finer septa which branch and anastomose to subdivide the " parenchyma " incompletely into ill-defined areas of quite variable size and shape. This finer ramification of the " stroma " consists for the most part, and in some areas almost exclusively, of thin-walled blood-vessels having an inconspicuous fibrillar backing to their endothelium, and this " stroma " is not sharply distinguishable from the parenchyma, there appearing to be all transitions from the endothelial elements of the " parenchyma " to the collagen-forming fibroblasts of the " stroma ".

The " parenchyma " occurs as islands and strands of rather closely packed cells having a moderate amount of faintly basophilic cytoplasm, relatively large oval nuclei of the vesicular type but with variable degrees of hyperchromatosis, a delicate nuclear membrane, and nucleoli which are usually so inconspicuous as not to be readily distinguishable from " false nucleoli " or particles of the nuclear basichromatin. Only in individual cells may the nucleoli be moderately increased in size, and even then they are only of a very limited prominence (maximum n : N ratio = 1 : 16). Here and there the nuclei may be closely aggregated in groups of half-a-dozen, no cytoplasmic boundaries being distinguishable. Over the greater part of the tumour the parenchymal islands are solid (Fig. 137A, below, and Fig. 138). But in considerable areas the elements may be arranged to surround blood-filled spaces, to which they form a wall from one to four cells in thickness (Fig. 137A, above). The contained blood is, to all appearances, in free circulation and in it free neoplastic cells occur. Areas of haemorrhage from these channels occur towards the surface of the tumour. From the smaller septa of the " stroma " a delicate system of reticular fibrils passes between the neoplastic cells, but it is not conspicuous, even in Mallory-stained sections. There is as a rule no condensation of this reticulum in connection with the vascular spaces; but in those parts where the trabecular meshwork is finer, the neighbouring septa themselves serve as such a backing. Where the stroma forms such a fine meshwork it may also occur that one wall of a blood-space is formed by neoplastic endothelium and the other by the " stroma "; or vascularised strands of " stroma " may transect such a blood-space. The internal layer of the neoplastic cells lining the large blood-spaces may be definitely flattened and then indistinguishable from adult vascular endothelium. More often, such flattening does not occur. One small focus was found showing rapid growth (e.g. 3 mitotic figures in a single oil immersion field) and here the vascular spaces are of small size, approaching capillary dimensions. The resulting appearance is much like that of the capillary endothelioma in Case 1. Here and there continuity could be traced between the neoplastic endothelium and the lining cells of blood-vessels of the " stroma ". Large areas of necrosis occur in parts of this tumour. In large parts of the tumour mitoses are not frequent and even where strands of cells are infiltrating between the muscle fibres of the myocardium (Fig. 138) one may search many fields before finding a dividing cell. A count made in a section showing more active growth gave a mitotic index of 3.

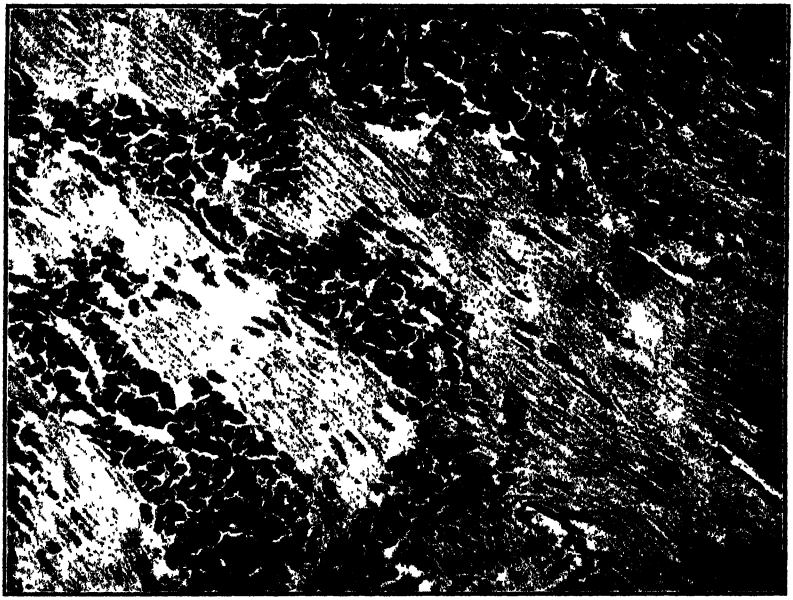

FIG. 138.—Invasion of the myocardium by the endothelioma shown in figs. 137 and 137A: Solid strands of neoplastic endothelium penetrating the musculature. (5144; 250 ×).

Remarks.—The features of this tumour of most interest to us in this discussion are the great predominance of solid growth over lumen-formation, and even where the latter occurs it is but seldom that actual vessels are formed; more often the disposition of the neoplastic cells merely allows the circulation of blood among them.

There is in this case no clear distinction of a " stroma " and " parenchyma "; and the " stroma " can scarcely be considered as non-neoplastic, for there is continuity between the endothelium of its blood-vessels and the endothelium of the " parenchyma ", and it is quite impossible to separate the finer bands of " stroma " from the " parenchyma ". The character of the " stroma " is largely altered by its participation in the organisation of fibrinous masses resulting from haemorrhage. One might describe this as an almost purely solid endothelioma, the blood-vessel formation being confined to small portions and being quite rudimentary .

Diagnosis.—Solid (and partly haemangioplastic) endothelioma of the myocardium.

Case 3 (*Bovine*, 11070).

The specimen consisted of a walnut-sized enlargement of one ot the cusps of the pulmonary semilunar valve of an ox. On section the greater bulk of this enlargement is seen to consist of blood. It lies in the subendocardial tissue.

Microscopically, beneath the endocardium of the valve is a considerable increase of collagenous tissue which forms a thick band enclosing the tumour tissue proper from the serosa of the endocardium on the one hand and from the myocardium on the other. It is, however, difficult to speak of this as an encapsulation, because as one follows this connective tissue inwards, it becomes gradually more cellular and becomes confused with the neoplastic tissue itself, from which it is by no means clearly demarcated; further, the border of this tissue against the myocardium is not a sharp one; it extends a short distance between the bundles of the myocardial fibres and was actually described here as a localised fibrosis of the myocardium. The neoplastic tissue consists of endothelial-like cells which in many places become confused with strands of collagen-forming cells, between it and which there are all transitions: one cannot speak of a clear separation of stroma from parenchyma, or of parenchyma from capsule. The neoplastic endothelial-like cells may be arranged in the following ways: (*a*) as a lining to small blood-spaces or vessels of approximately capillary dimensions and which are filled with blood-cells. These small vessels may be more closely set or more widely separated in the solid tissue to be described; (*b*) as a lining to moderately (e.g. diameter 250μ) or greatly enlarged (e.g. diameter 1 cm.) blood-spaces, also distended with blood. Into the latter occasionally occur papilliform invaginations or ingrowths of their walls; (*c*) as solid tracts or strands of cells which sometimes show transitions to areas (*a*) in the form of small concentric whorls of cells or imperfect lumen-formations. These cells are not demarcated from contiguous strands of fibroblast-like cells constituting " stroma " or " capsule ".

The tumour cells are oval to spindle-shaped and are flattened. Their nuclei are variable in size and vary in shape from short-oval to elongate-oval; it is especially the cells with the latter form of nucleus which become confused with the collagen producing fibrocyte-like elements. The nuclei have delicate membranes and a very finely divided chromatin; they appear vesicular. One, two, or more nucleoli are visible, but are usually not easily distinguishable from small nodal accumulations of basichromatin (" false nucleoli ") on the chromatin network. These nucleoli are not prominent and not distinctly acidophilic. However, more prominent nucleoli do occur, especially in the solid areas (*c*) where they are quite regularly prominent and distinctly acidophilic ($n : N = 1 : 9$); they may even be altered in shape—ovoid, rod-shaped, or even slightly lobed or irregular in outline. Similar features may be seen in the nuclei of the cells lining blood-spaces (*a*) and (*b*), although less often. Occasionally, kidney-shaped or pyriform nuclei may be seen, and not a few nuclei show irregularity of outline due to serrations of the nuclear membrane. Sometimes quite irregularly lobed nuclei (possibly indicative of amitotic divisions) are found. In the solid areas (*c*) where anaplastic changes are most marked, the nuclei tend to be smaller (long diameter 7μ) and more approaching a spherical shape than in the angioplastic parts, where the nuclei are usually some 16μ in long diameter. In parts there are considerable numbers of infiltrating, haemosiderin-laden macrophages, in others a few infiltrating neutrophiles and plasma cells occur. There may also occur free erythrocytes among the neoplastic cells. Here and there are small foci of calcification. Occasionally, in those areas intermediate between the endothelial-like " parenchyma " and the connective-tissue-like " stroma ", small foci of myxomatoid tissue occur (widely separated stellate cells): the elements here are undoubtdly also tumour cells, on account of the abnormal prominence of their nucleoli.

Remarks.—Originally a diagnosis of haemangioma was made, showing that the observer was impressed with the predominant angioplasia. But on account of the large areas of high cellularity and the distinct anaplastic changes, this diagnosis cannot be supported according to the nomenclature we are using. The tumour is an endothelioma which is predominantly angioplastic, giving rise both to neoplastic capillaries and to cavernous blood-spaces, but also partly solid. The myxoma-like transformation of small areas of the " stroma " is interesting in demonstrating the further potentialities of the tumour cells, the " stroma " itself being considered as a part of the neoplastic tissue in this case.

Diagnosis.—Angiogenous endothelioma (predominantly haemangioplastic, but in parts also solid) of the pulmonary semilunar valve.

Case 4 (*Equine*, 14714).

The subject was an aged female mule, seen through the courtesy of Dr. G. Martinaglia, who removed by operation a fist-sized rounded tumour situated on the off thigh over the proximal portion of the semitendinosus muscle (Fig. 139).

Microscopically (Figs. 140 and 141), the tumour is seen to lie in the subcutis and is well encapsulated from the overlying skin and underlying muscle. It is pervaded by coarse strands of collagenous tissue continuous with smaller strands of collagen-forming cells which are not clearly demarcated from what, under low magnification, appears to be the "parenchyma" enclosed by them. The latter is composed of elements resembling endothelial cells—spindle-shaped to oval cells, with oval to rounded vesicular nuclei which may be slightly indented on one side, and one to two nucleoli which are rather prominent for endothelial cells (n : N often 1 : 25 to 1 : 16). As seen in Giemsa-stained smears, also, these cells have distinct endothelial characters: weakly basophilic and clear cytoplasm, typical leptochromatic and amblychromatic nuclei with finely-divided chromatin and palely-staining nucleoli. The cells have in many places a somewhat characteristic but variable arrangement (Fig. 141): in single or double rows between the adjacent collagen forming cells (interfascicular type of Ewing); in solid nests, clumps or even sheets (diffuse type of Ewing). In these nests a distinctly concentric arrangement of the cells is often seen and in some of these whorls a minute lumen accommodating a single (circulating) erythrocyte (which is usually deformed in order to squeeze through the very restricted space) may be seen on examination with the highest magnification. Or the cell boundaries may be lacking and many nuclei packed closely together in a single mass of cytoplasm. Lumen-formation is restricted to these spaces of strictly capillary dimensions, and with it is not to be confused the appearance seen in paraffin sections of much larger spaces around which the tumour cells are flattened and which appear empty (Fig. 140): these were at first taken for evidence of lymph-vessel formation, but frozen sections show that they are actually surviving fat cells of the subcutis around which the neoplastic elements grow most intimately and become compressed, closely simulating lumen-formation. Larger

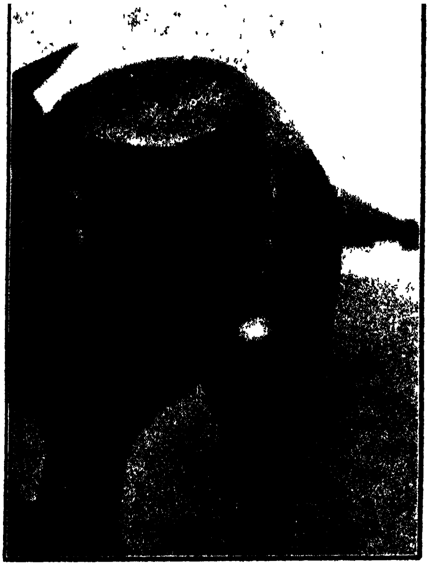

FIG. 139.—Haemangiogenous endothelioma of the subcutis of a mule. (14174).

blood-vessels occur in the collagenous tissue which forms a support for the endothelial-like elements. As has been said there is no distinct demarcation of this tissue from the endothelial-like elements; the transition appears to be a gradual one, and the endothelium of the vessels in this tissue often appears more prominent than usual. Mitotic figures are not frequent, the index being less than 1.

Remarks.—This tumour grows almost entirely in solid form, evidence of lumen formation being seen only on close study.

Diagnosis.—Haemangiogenous endothelioma growing almost entirely as endothelioma solidum.

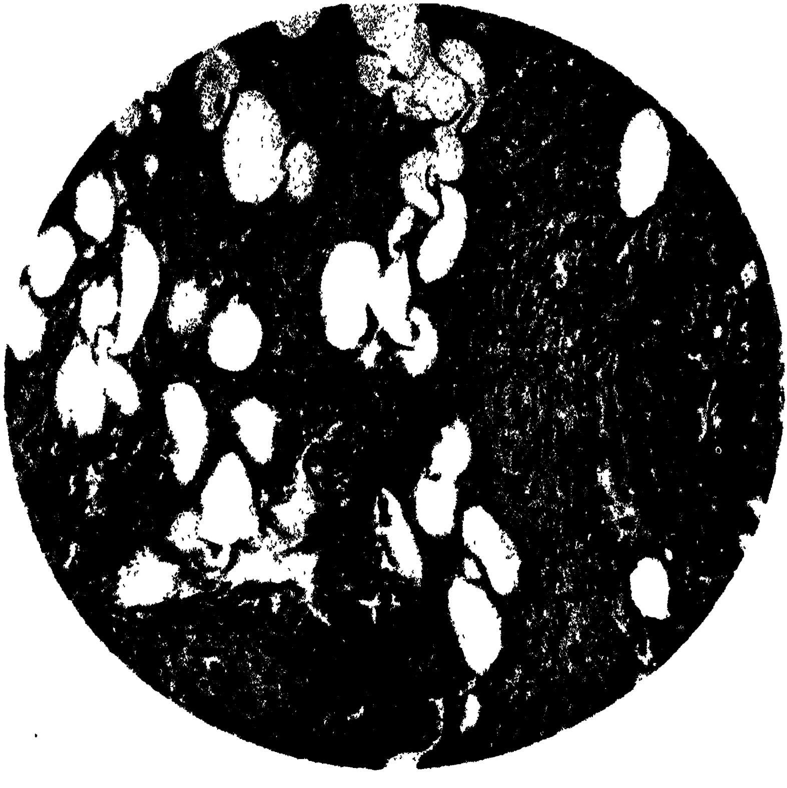

FIG. 140.—Structure of the endothelioma of a mule shown in fig. 139: Solid type of growth (*E. solidum*) invading between the fat cells of the subcutis. (14174: 240 ×).

Case 5 (*Ovine*, 5847).

The subject was a sheep, stated to have been emaciated and to have been obviously ailing for a few days, and from which the liver and spleen were submitted to Dr. R. J. Ortlepp (of this Institute) by a native, who noticed no other affection of the carcass. For the naked eye appearances, I draw on Dr. Ortlepp's description: "The fresh liver was of a yellowish-red colour and about half again as large as normal and of firm consistence. The surface was dotted all over with reddish spots and patches, some of which had a white rim; these varied in size from that of a pin's head to about half the size of a threepenny-bit. On section, the organ was seen to be riddled with red spots. . . The spleen was of a dark red colour and full of foci somewhat similar to those in the liver ".

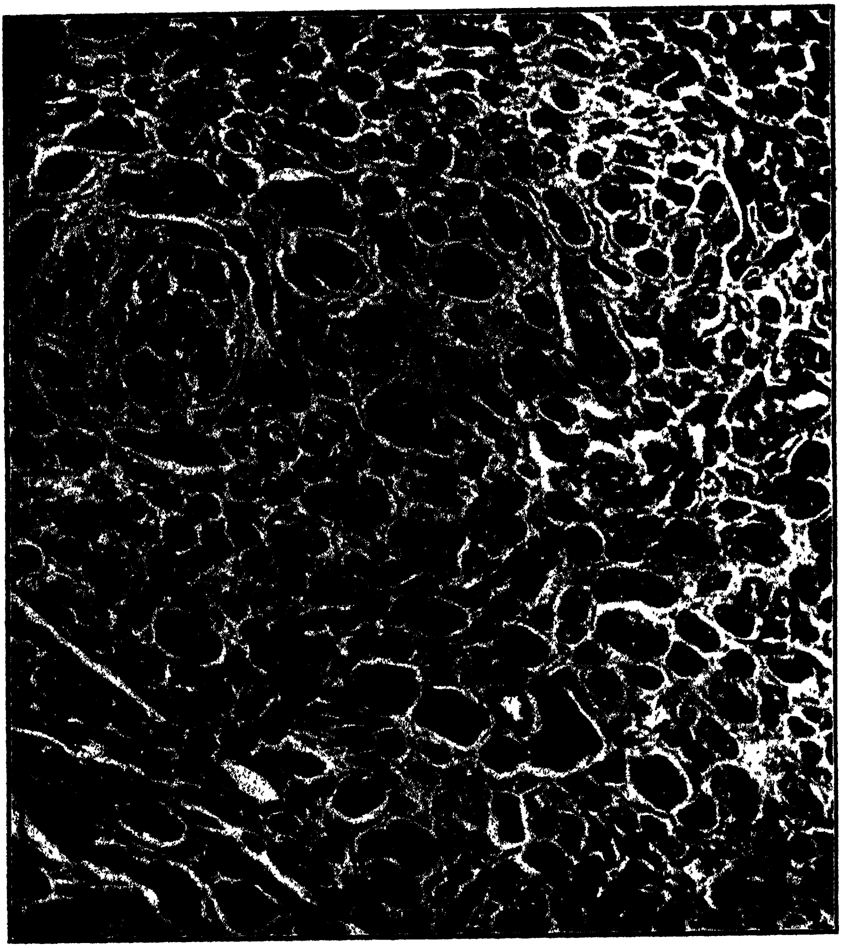

FIG. 141.—High magnification of the endothelioma of a mule shown in figs. 139 and 140: Whorls of neoplastic endothelial cells with very rudimentary lumen-formation (solid and capillary haemangioplastic type of growth). (14174; 500 ×).

Microscopically (Figs. 142 to 145), the liver shows pronounced structural alterations which, although for convenience to be described under separate headings, must be understood as being only artificially separable, all intermediate grades existing:—

(*a*) Multiple circumscribed foci often some ·5 cm. in diameter and having a well developed capsule, some 120μ in thickness, which walls off from the surrounding liver parenchyma a highly cellular tissue in which collagenous stroma is not demonstrable. The cells are either arranged to surround and to line large spaces (up to 600μ in diameter) containing (circulating) blood; or in other parts they form a more solid tissue, which is, however, often excavated by smaller blood-channels which are ill-defined and vary in size down to those of capillary dimensions, allowing only one or a few red cells to pass abreast. The cell boundaries are poorly defined and the appearance of a syncytium results; or when they are better defined, it can be judged that the predominating cell-shape is stellate, although (in section) many of the elements appear spindle-shaped.

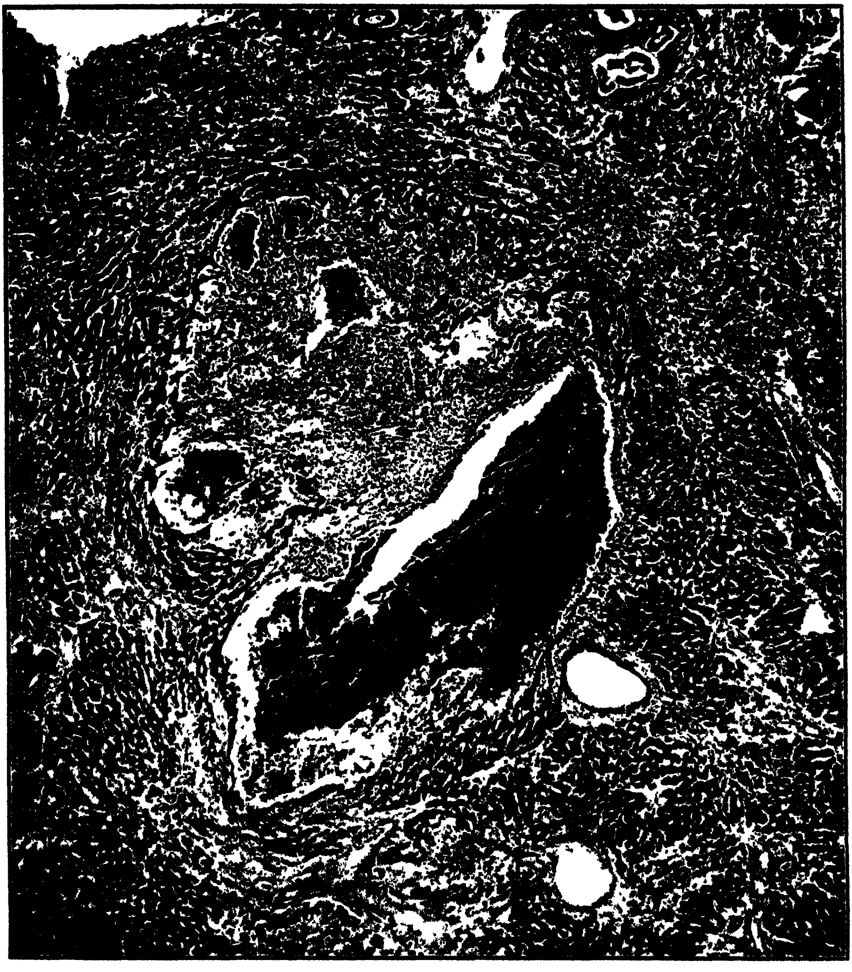

FIG. 142.—Reticulo-endothelioma of the liver of a sheep; one of multiple foci: Note continuity with the proliferating reticulo-endothelium of the hepatic sinusoids and the haemorrhages which result from the escape of the blood contained in the neoplastic capillaries. (5847; 33 ×).

The cytoplasm is moderate to large in amount, is prolonged into processes, and with haemalum-eosin stains a light mauve-pink and has a faintly granular or cloudy appearance. The size of the cells varies greatly, the larger ones measuring *ca.* 30μ in diameter. The nuclei conform to the distinctly vesicular type; they have a fairly sharp membrane enclosing a rarefied and delicate chromatin network, sometimes with a few coarser particles on its nodes, especially in the submembranal zone (hyperchromatosis). There are one to two nucleoli which are in general very inconspicuous, but here and there occur nucleoli reaching a diameter of 2·8μ. Gross nucleolar irregularities are rare but occasional examples of such were seen, e.g. an elongated, pyriform nucleolus measured 10μ in length—half the length of the nucleus. The nuclei are most variable in shape, a phenomenon which does not impress one as a sign of anaplasia but rather as an expression of a fundamental elasticity in the type-shape of the nucleus. The majority are short-oval to elongate-oval (cigar or spindle-shaped). Many are bean-shaped. Other forms—pyriform, polygonal, indented—characterise the minority. Some of these

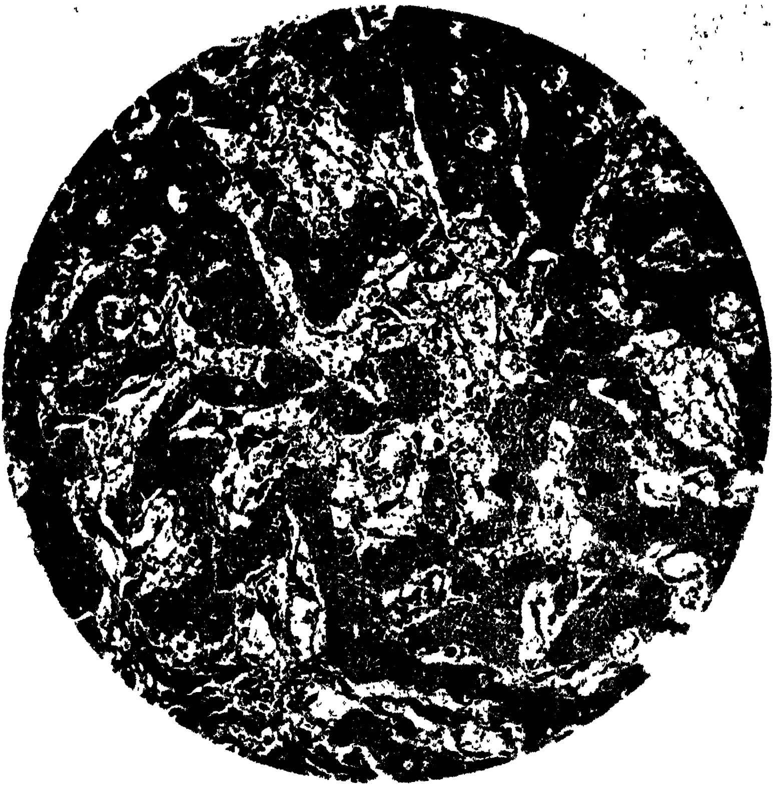

FIG. 143.—Early stage of the foci represented by fig. 142: Hyperplastic reticulo-endothelium of the hepatic sinusoids. (5847: 250 ×).

irregularities are associated with the pressure of included groups of crystals of haematogenous pigment, appearing as small spicules about 3μ in length and lying in vacuoles which cause concavities on the nucleus. Rarely, bi- or multi-lobed nuclei occur. Those cells immediately lining the blood-channels tend to be flattened, resembling endothelial cells (or littoral reticulo-endothelials), and these often show a heavier pigmentation—spicules and granules (greenish yellow with haemalum-eosin and golden with *Berlinerblau*) may be diffusely scattered through their cytoplasm. Free (desquamated) elements of the same nature are common among the blood-cells in the lumina. With Mallory's triple stain (Fig. 144) one sees, throughout, a rich network of reticulum fibrils intimately associated with the peripheral portions of the cell cytoplasm and its processes, and delineating the vascular spaces.

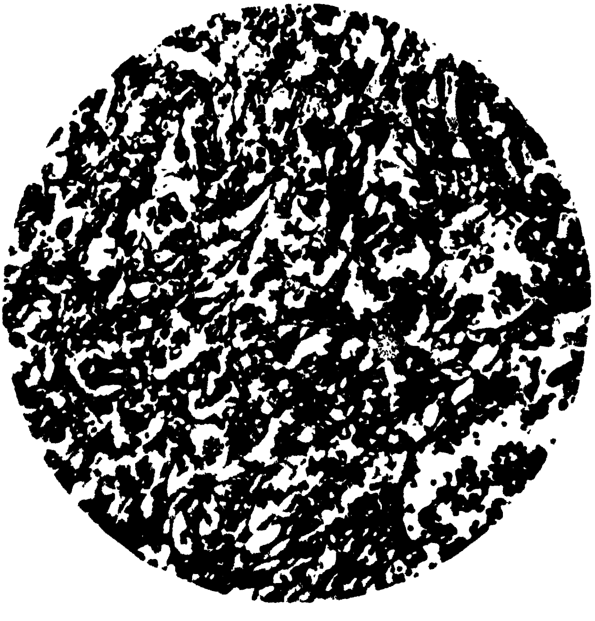

FIG. 144.—Close association of reticulum fibrils with the neoplastic endothelium of a focus of reticulo-endothelioma of the liver such as shown in fig. 142 : Mallory's "triple" stain. (5847 : 240 ×).

(*b*) Similar encapsulated foci in which the cellular walls of the vascular spaces have completely or largely disappeared and the blood has formed a thrombus: these are simply small haematomata resulting from degenerative changes in the neoplastic tissue. Traces of the reticulum can still be seen separating the blood into compartments and indicating the position of the erstwhile vessel-walls. Fibrin has been laid down and the erythrocytes appear largely as "ghosts". At the periphery of such foci the neoplastic tissue as in foci (*a*) may still persist.

(*c*) Foci similar to those described under (*a*) except that they are not encapsulated and are poorly circumscribed and a good deal smaller (Fig. 142). At their edges, these foci penetrate intimately into the surrounding hepatic tissue and merge into—

(*d*) A relatively diffuse hyperplasia affecting the Kupffer cells of the hepatic sinusoids (see Fig. 142). This is best seen radiating from the periphery of the foci (*c*), between which and the areas (*d*) all intermediate stages exist; i.e. there is a tendency for this (diffuse) hyperplastic process to be especially manifest in ill-defined foci (Fig. 143), or, in other words, it appears that a more diffuse hyperplastic process reaches definitely neoplastic grade only at certain focal points:—In some parts of the liver one is struck merely by the prominence of the littoral cells of the intralobular sinusoids and by their increase in number. Elsewhere one may see a proliferation of these elements between the sinusoidal lumen and the adjacent liver-cell-cords, so that between the former and the latter two, three, or four strata of elements of the reticulo-endothelium may exist, of which only that adjacent to the circulating blood consists of flattened (littoral) elements. And such areas, as had been said, pass over into more definite focal proliferations. The cells are similar in all respects to those of the latter.

(*e*) In many parts of the liver this type of proliferation of sinusoidal elements associated with reticulum formation is replaced by proliferation of collagen-forming spindle-cells producing a fine cirrhosis.

The spleen shows focal changes (Fig. 145) similar to those described under (*a*) and (*c*) in the liver. But encapsulation is somewhat deficient—it appears to be largely limited to an increase of connective tissue in pre-existent trabeculae of this organ and such trabeculae may be invaded by the neoplastic cells, with the result that massive protrusions of the latter into the trabecular veins may be seen, together with actual growth along the intima; here the venous endothelium becomes replaced by neoplastic cells or else joins them (?) in a proliferation whereby is formed a lining of several cell layers to the vessel. In the venous blood, desquamated neoplastic elements may be seen. Where no trabeculae limit the neoplastic tissue, the cells thereof appear to merge gradually with the reticulo-endothelium of the spleen, which throughout the red pulp is hyperplastic and much mobilised to form macrophages (" splenocytes "). For the rest, the foci are very similar to those of the liver, except that, as would be expected, the blood enclosed in the neoplastic vascular spaces is richer in white cells, especially lymphocytes. Regarding the white pulp of the organ, the Malpighian corpuscles show a prominence of reticulum cells and macrophages; and striking evidence of erythropoiesis is seen in the shape of the very large numbers of erythroblasts and (especially) normoblasts to be found in the lymphoid tissue. The red pulp is much congested with blood. In both hepatic and splenic foci, mitotic figures can be found only here and there.

Remarks.—The type cell concerned in this neoplastic process is the reticulo-endothelial cell, as is clearly shown by the morphology with ordinary stains (variation from stellate cells in syncytial arrangement to flattened littoral elements), the constant and intimate association of the cytoplasm with a prominent fibrillar reticulum, the marked phagocytic capacity in respect of haematogenous pigment, and the actual continuity with Kupffer cells of the liver and the reticulo-endothelium of the spleen. In the human literature, Ewing (p. 736) is very conservative regarding the possibility of the development of sarcomatous neoplasms from hepatic endothelium and warns against accepting as mesoblastic neoplasms (angiosarcomata) those cases of hepatoma in which the epithelium is very anaplastic and in which the tendency to excessive vacularization and even to actual endothelial proliferative overgrowth is well known (" haemorrhagic hepatoma "). Although these objections are obviously inapplicable here, it is of interest to mention them as illustrating the apparent rarity (even to the point where authorities doubt their occurrence) of lesions similar to this in man. From the point of view of certain fundamental resemblances of the actual histological processes, one may here also recall Gaucher's disease, in which occurs a marked splenic enlargement due to overgrowth of the reticulo-endothelial elements of this organ as well as in other blood-forming organs. In that disease also, foci may appear in the liver (in the portal canals, however), regarding whose primary or secondary (metastatic, depending on embolism) nature there is a difference of opinion. It is classed by Ewing as a tumour-like hyperplasia of endothelium intermediate between inflammatory and neoplastic overgrowth—(cf. in the present case the accompanying proliferation—arising from the same elements as give rise to the tumour cells and the tumour-like hyperplasia of

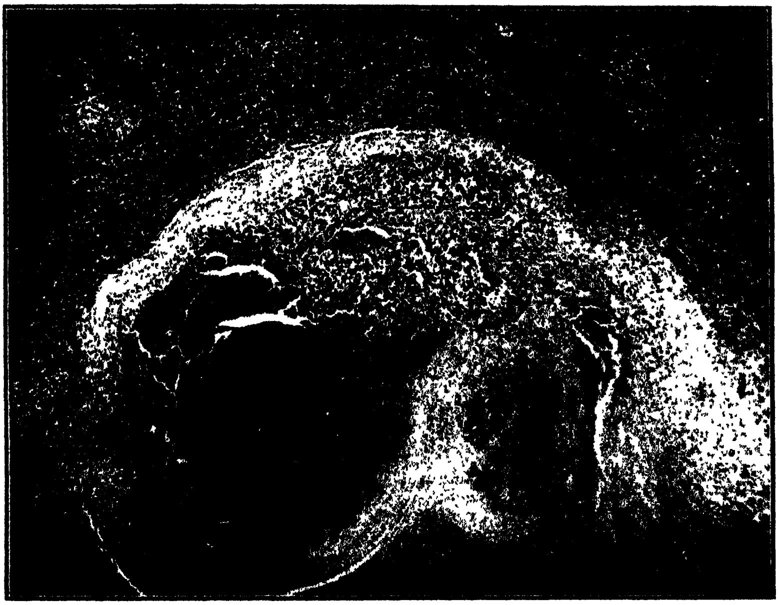

FIG. 145.—Reticulo-endothelioma of the spleen of the sheep: One of multiple foci affecting both this organ and the liver. (Same case as figs. 142 to 144). (5847; 33 ×).

reticulo-endothelial nature—in the form of fibroplastic tissue, producing cirrhosis). He further remarks that "the cells lack the hyperchromatic nuclei of tumour cells, and they carefully respect anatomical barriers(⁶)", the latter feature being in pronounced contrast to the lively invasive propensities which are exhibited by the tumour cells in regard to the thick trabeculae of the spleen in this case. It must also be remarked that, fundamentally, the lesions under discussion present certain histological features in common with Hodgkin's disease. The whole question of Hodgkin's disease, "reticulum cell sarcoma" of lymphoid tissue, Gaucher's disease, and monocytic leucaemia (reticulo-endotheliosis) in man is still shrouded in mystery. In animals we are on even less safe ground, although it seems likely that some of these more obscure conditions encountered in the domesticated species may have a significance for the human pathologist.

My impression of the present case was that one has to deal with multiple primary tumours of liver and spleen, which, although not secondary one to the other, far from being independent, represent the culmination at focal points of a diffuse systemic hyperplastic (⁷) affection of the reticulo-endothelium in these two organs, whose interdependence has in recent years been increasingly emphasized by McNee (1932).

After some hesitation I have classed this case tentatively with the haemangiogenous endotheliomas. It would appear to have many features in common with the multiple liver tumours described in a woman by Vidari (1933) and in an infant by Foot (1927). Its histology and cytology are clear; and although there is a considerable tendency, on physiological grounds (especially from the standpoint of blood-formation and blood-destruction), to differentiate sharply between reticulo-endothelium and the general vascular endothelium, on both embryological grounds and the grounds of normal and neoplastic morphology of the cells concerned it is hard to see fundamental differences. We know that even the general vascular endothelial cells, in respect both of potentialities (reticulum fibril-formation, etc.) and physiology, are hard to separate sharply from reticulo-endothelium: not only may reticulum fibres be demonstrated, for example in the endothelium of the renal glomeruli (Allen, 1927; see also Corner, 1920), not only do we still speak of the intralobular *capillaries* of the liver, not only is reticulo-endothelium in continuity with the general vascular endothelium; but it is hard to establish that even as regards haemopoietic and phagocytic functions the two types show differences except of degree. In ordinary endothelioma, the elements are also intimately associated with reticulum fibril-production; they show transitions to the fibroblastic type of cell, and even (as we saw in one case) to stellate cells of myxoblastic character. Thus one can hardly contend that by any of these criteria, admittedly prominent in the present case—phagocytosis, fibril-production, or variation in cell-shape and arrangement—can tumours derived from

(⁶) It is hard to see why lack of such features, characteristic only of *malignant* tumours, should be advanced as evidence against a neoplastic nature of lesions.

(⁷) Cf. the widespread focal appearance of leucotic and leucaemic lesions.

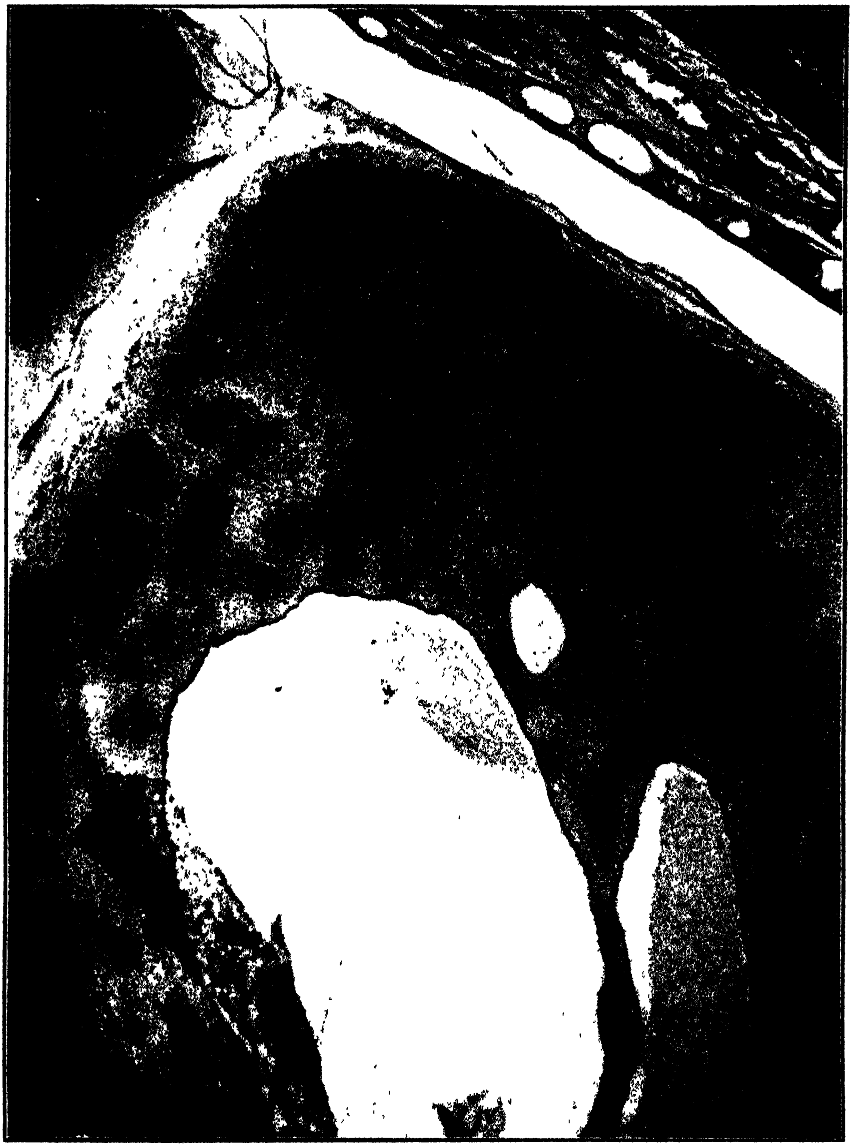

FIG. 146.—Lymphangiogenous endothelioma of the subcutis of a dog: Encapsulation from the overlying skin (above, right); largely solid type of growth in which occur whorls of endothelial cells; occasional larger and smaller lymph-containing cysts. (9061; 33 ×).

reticulo-endothelial cells be contrasted with those derived from the general vascular endothelium. If we are to class such tumours with sarcoma (" reticulum-cell sarcoma ", " reticulo-endothelioma ") it is hard to see how we can avoid a reversion to the old practice of classing all malignant endothelial tumours as sarcomata. Such a unification may perhaps occur in the future, when the rôle of the reticulum-cell in lymphoid tissue and in lymphosarcoma may be fully elucidated; but that time is not yet ripe.

Diagnosis.—Multiple angioplastic endothelioma (arising from the reticulo-endothelial cells) of the liver and the spleen.

(*b*) LYMPHANGIOGENOUS ENDOTHELIOMATA.

Case 6 (*Canine*, 9061).

The subject was a dog from which a tumour, stated to have developed at the site of a gun-shot wound (lead pellet), was removed. The specimen consists of a broadly-pedunculated ovoid tumour of the subcutis, thinly encapsulated and covered by skin. It measures 4 x 3 x 2·5 cm. On section the (fixed) tumour tissue has a greyish-white colour and a soft (gland-like) consistence. For the most part it appears solid but in some parts is permeated by a number of cyst-like spaces not containing blood and varying from 0·5 to 5 mm. in diameter.

Microscopically, the neoplasm is seen to lie in the subcutis and is distinctly encapsulated from the overlying skin (Fig. 146, above, right). Occasional septa of loose collagenous tissue with blood-vessels run through it (Fig. 146, above, left), and these may sometimes be invaded by the neoplastic tissue. The many other strands and tracts of collagen-forming tissue which occur in the tumour and which at first glance might be taken for a stroma are seen, especially on cytological study and the application of fibrillar stains, to be a part of the neoplastic tissue itself. They will be described later. The neoplastic tissue (Figs. 146, 147, 148) is composed of: (*a*) a highly cellular tissue whose elements are closely packed and arranged in small, rounded to oval, concentric whorls (Figs. 146, left, 147) usually varying in diameter from 130 to 300μ, but sometimes also forming larger, more diffuse tracts or lobules of cells without concentric arrangement. The cells are indistinctly outlined, oval to spindle-shaped elements having short-oval to elongate-oval nuclei which vary in long diameter from *ca.* 7μ to *ca.* 19μ. Although the nuclei vary a good deal in shape—e.g. some may be indented, kidney-shaped, or twisted—signs of anaplasia are almost absent and the texture of the nuclei is very uniform: they have a delicate membrane enclosing a pale-staining, finely and evenly divided chromatin. Nucleoli are scarcely visible and may be confused with the small knots of basichromatin which can sometimes be seen; they stain poorly, and a n : N ratio of 1 : 50 is never exceeded. The whorls consist of a central group of cells, disposed irregularly and tending to have plumper nuclei, surrounded by many concentric layers of curved elongated cells tending to have more elongated nuclei: the transition is very gradual and the cells all unmistakably of the same type. They are intimately associated with a network of reticulum fibrils which, more rarefied in the centre of the whorls, becomes more prominent as the periphery is approached (Fig. 148). At the latter, the cells merge gradually into (*b*) spindle-shaped elements (Fig. 146, centre and right, Fig. 147) which are set farther apart because they are associated with the production of collagen. This whole fibrillar system—reticulum and collagen—is continuous. The spindle cells form the wide tracts and stands superficially resembling a stroma, as was mentioned earlier, or which support the whorls or surround the more diffuse areas of endothelial-like elements. They show all transitions, from the latter, to fibrocytes

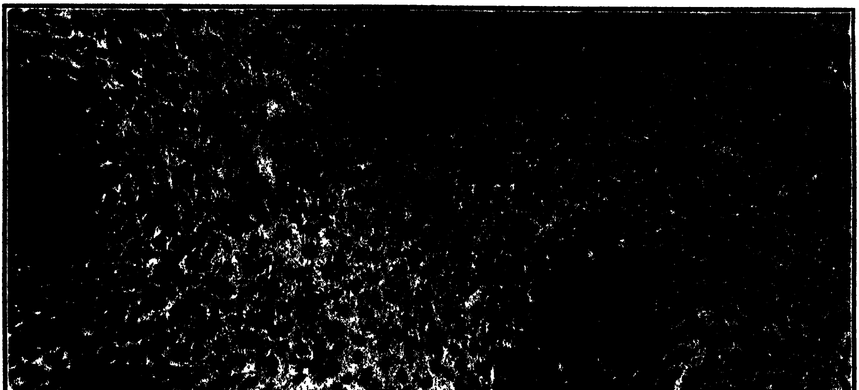

FIG. 147.—Detail of the structure of the solid portions of the canine lymphangiogenous endothelioma shown in fig. 146: Whorls of endothelioid cells in continuity at the periphery with diffusely-growing spindle cells associated with fibril-production and more of fibroblast type. (9061; 250 ×).

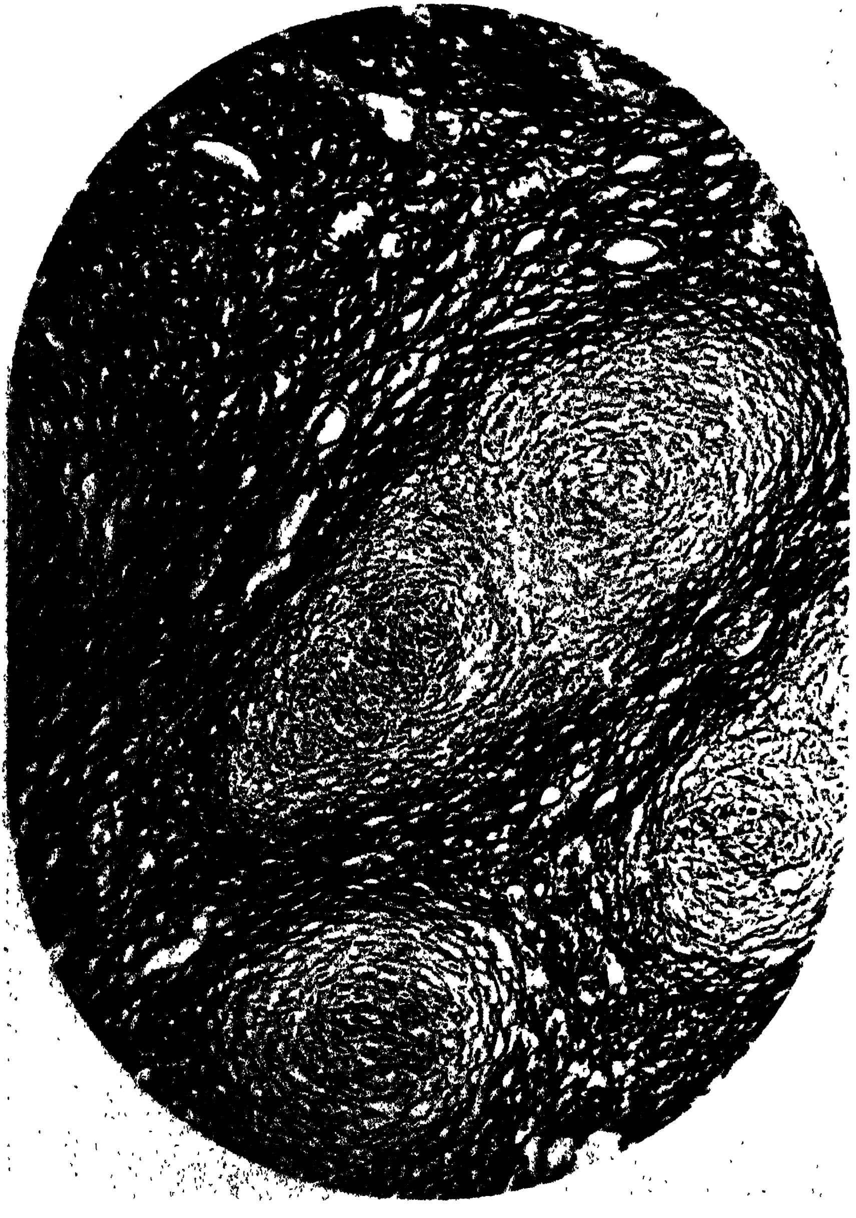

FIG. 148.—Application of Mallory's fibrillar staining to the tissue shown in fig. 147: Well marked reticulum production in the whorls of endothelial cells with gradual transition to the collagenous fibrils produced by the diffusely-growing cells. (9061; 250 ×).

with smaller and narrower nuclei. In these tracts blood- and lymph-vessels occur accompanied by a small amount of adventitial collagenous tissue: these (together with the occasional loose septa mentioned previously) constitute the stroma proper of the neoplasm. But besides these (non-neoplastic) vessels, there occur large spaces filled with lymph (Fig. 146, below). The walls of these are formed by the fibroplastic cells and are lined by endothelial elements continuous with and not easily distinguishable from the latter; the condensation of cells which forms this lining may be one or several layers in thickness. In some parts of the tumour only there may be a variable admixture of erythrocytes with the lymph.

Mitotic figures are confined to the non-collagenous tissue and are erratic in their distribution: in many whorls none are to be seen; on the other hand three were seen in a single whorl. A count made at random over both types of tissue gave an index of 3.

Summary.—A circumscribed tumour of the subcutis composed of an inconspicuous stroma and a parenchyma arranged chiefly as solid whorls of cells of endothelial type without lumen-formation; these cells, which produce reticulum-fibrils, are everywhere transitional to tracts of cells which produce collagen and which again go over to endothelial elements lining neoplastic lymph-spaces.

Diagnosis.—Solid and lymphangioplastic endothelioma (lymphangiogenous endothelioma).

Case 7 (*Bovine*, 8124).

No complete macroscopic description of the lesions can be given. This specimen consists of neoplastic nodules which were attached to the capsule of the spleen of a bovine slaughtered at the Germiston Abattoirs. Of these nodules, some are rounded and discrete, measuring *ca.* 2 cm. in diameter and showing a fairly prominent fibrous stroma supporting a softer greyish tissue. They are firm in consistence. Others are flattened close aggregations of broadly attached or somewhat pedunculated nodules which individually vary in diameter from 1 mm. to 1 cm., are separated one from another by deep clefts, and form plaques reaching a diameter of 4 cm. Their surfaces are covered by serosa (smooth and glistening).

Microscopically (Fig. 149) the discrete nodules lie in the (splenic) subserosa in which they tend to be circumscribed by a loose-textured collagenous capsule. However, in many places the latter is lacking superficially, and the tumour extends to immediately below the covering mesothelium, filling out the whole thickness of the subserosa. The tissue consists of a well-developed but most irregularly arranged system of connective-tissue bundles (i.e. there is a fibrosis of the visceral peritoneum) which indistinctly demarcate areas of cellular parenchyma. These areas are composed of elongated cords of cells, one or two elements in thickness, which are supported by a variably developed but usually rich system of fine collagenised strands of connective tissue; between the cells of these solid cords, reticulum-fibrils are demonstrable and are in intimate continuity with the collagen fibrils forming a "stroma" between the cords. In most parts this parallel arrangement of rows of cells between strands of collagen is a very striking feature of the morphology. In other parts the strands may be several rows of cells in thickness and there is often a tendency for the nuclei to be aggregated in a small clumps, without cytoplasmic demarcation being demonstrable. Although definite whorls are not formed, this appearance is very similar to what has been described in other endotheliomas. The tumour cells are somewhat variable in morphology, but are all clearly of the same type and have in general a close resemblance to endothelial cells. In general they are polyhedral elements of moderate size and (in paraffin sections) often measuring some 7 to 11μ in diameter. Many, however, show distinct traces of a greater specialisation in form: in the strands or rows of cells it is often seen that they assume a cuboidal or even columnar shape (i.e. they are elongated in a direction vertical to that of the length of the strand), resting with a broad base against the collagenous stroma; on the other hand, the cells very often tend to a spindle shape (being elongated in the same direction as that of the length of the strand), and there is a tendency for the cell strands to enclose lumina of capillary dimensions containing a neutrophil-rich lymph-like fluid. The cytoplasm inclines to a weakly basophilic reaction, except in degenerating cells with pycnotic nuclei, in which it is strongly acidophilic. It appears homogeneous and of but a slight degree of density. The nuclei fill at least one-half of the cytoplasm, in which they are often somewhat eccentrically situated. They are usually of short-oval shape, less often elongate-oval. They

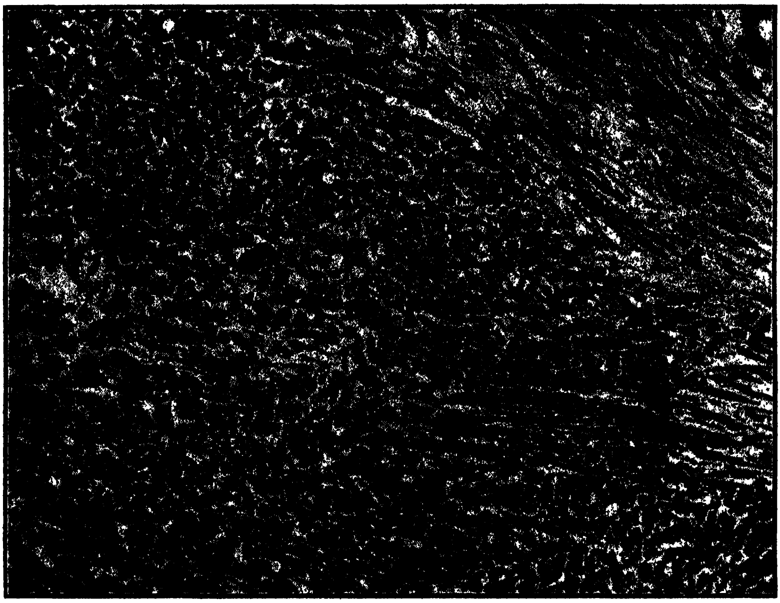

FIG. 149.—Detail of the structure of lymphangiogenous endothelioma: Elongated rows of cells with occasional rudimentary traces of capillary lumen formation. (8124; 240×).

measure mostly some 6μ in long diameter, but more elongate ones may reach a length of more than 10μ. Minor irregularities in shape (angularity, slight serrations of the nuclear membrane, etc.) are often seen. The more typical nuclei are only very moderately or even but slightly chromatic, showing a fine, regular network. However, in most parts there is a severe infiltration of neutrophils (associated with the tumour tissue in the vicinity of completely necrotic areas) and in these regions the nuclei often appear richly chromatic (necrobiotic hyperchromatosis and pycnosis), a phenomenon which is not to be interpreted as anything more than a secondary change in essentially amblychromatic nuclei. The single or (equally often) double nucleoli are often moderately to markedly eccentric in location and are fairly prominent structures, especially in the non-necrobiotic regions; n :N ratios of 1 : 9 to 1 : 14 are frequently seen; in most nuclei, however, the ratio is nearer 1 : 25.

On the surface of the papilliform nodular plaques described macroscopically, one can see the appearances of mobilisation of the mesothelial cells, but there is no continuity traceable between such cells and the tumour cells. On the other hand, at the edges of the lesions an unmistakable sprouting appearance of the tumour cells is seen, clearly reminiscent of the " budding " of capillaries. The mitotic index is 3.

Remarks.—In diagnosing this tumour it is essential to have clearly in mind the possibility of secondary serosal carcinosis or of (primary) mesothelioma. This differential diagnosis is not difficult if it is remembered that in both those conditions one expects to find evidence of an *intralymphatic* growth of the neoplastic tissue, whereas in this case the type of growth is *lymphatic*, i.e. resembling the budding of capillary lymphatics. Further, carcinoma is excluded by the resemblance of the cells to endothelials, the indistinct demarcation of " stroma " from " parenchyma " and the presence of intercellular reticular fibrils, and the absence of a marked degree of anaplasia. This tumour should be compared with the pleural lymphangiomas (equine 8045 and bovine 3589); its diagnosis is largely dependent on the similarity of its growth mode and cytology to the younger (solid and capillary) portions of such tumours.

Diagnosis.—Lymphangiogenous endothelioma of the visceral (splenic) peritoneum.

SUMMARY.

In considering the angiogenous neoplasms (" endothelioblastomas ") of the domestic animals, we have attempted to draw, as sharply as possible, a line of distinction between those of " benign " type (angiomata) and those of " malignant " type (endotheliomata). It must freely be admitted, however, that this separation is, in the present state of our knowledge, no easier (and indeed probably considerably more difficult) to carry through than is the discrimination between certain benign or malignant epithelial or connective-tissue tumours; it is easy only in the typical cases at the two extremes of the series.

Among the cases reported in some detail, attention may be drawn to the description of as many as four cases of that rare neoplasm, lymphangioma. The structure of all three varieties of this neoplasm—simple (capillary), cavernous and cystic—is represented by the specimens in the collection, but only the cavernous type was encountered in pure form (twice), the other two tumours being of mixed capillary and cavernous and mixed capillary, cavernous and cystic types respectively. The cavernous lymphangiomas give rise to no difficulty in diagnosis, but the less familiar lymphangiomas of predominantly capillary type raise a difficult question in their differential diagnosis from (lymphangiogenous) endothelioma: the circumstance that these tumours grow by means of solid capillary buddings or sproutings allows them to fulfil, in part at least, one of the criteria that are commonly used in the recognition of endothelioma, viz. that cellular proliferation predominates over angioplasia. But on closer analysis it is seen that this " predominance " is merely an apparent one, since the solid sprouts of cells are destined soon to acquire lumina, and the fields of solid growth therefore represent only a very transient phase through which the neoplastic units pass before becoming clearly recognisable as (neoplastic) vessels; non-neoplastic vessels grow in the same manner, as is well known. In making this distinction from endothelioma we have rather to rely on the absence of what may be described as a " permanent " cellular predominance, on the absence of invasive growth, and on the absence of conspicuous anaplastic cellular changes; although (as one might already expect from experience in other fields of tumour pathology) one may easily be led into error through an exclusive reliance on any one of such criteria alone. Further, it goes almost without saying that, ignorant as we are of the actual course of the lesions under consideration, their rigid classification into benign or malignant types is based on less certain grounds than could be wished. Certainly a naked eye distinction between certain tumours here termed angioma and others classed as endothelioma would by no means be possible in all cases. It is also likely that some authorities would class as angiomas tumours which in the Onderstepoort collection are grouped under the endotheliomas. This dilemma, which some pathologists attempt (perhaps more wisely) to evade by the use of the non-committal term " endothelioblastoma " for this whole group of neoplasms, is familiar even from the study of the much better known haemangiogenous tumours.

Of the cases of endothelioma, more especial interest attaches to the histological descriptions of endothelioma of the heart in bovines, of multiple (reticulo-) endotheliomatosis of the liver and spleen of the sheep, and of lymphangiogenous endothelioma in the dog and in the ox. The last-mentioned case is of especial importance, in demonstrating with clarity the distinction between lymphangiogenous tumours (endothelioma) of serous membranes and mesothelioma. Both this case and the two cases of lymphangioma of the serosae may profitably be studied in close association with the description of mesothelioma in Chapter VI. It is well to repeat here, in view of the fact that the distinction between these two kinds of tumours is so little recognised (cf. the application of the term " endothelioma " to mesothelial tumours as well!), that the essential difference lies in the *lymphatic* growth of the angiogenous serosal tumours as contrasted with the *intra-lymphatic* spread of the mesotheliomas. There are of course also many other differences of histological detail, and the two types can, at least in the ox, be distinguished with ease on naked-eye examination alone.

Nucleolar enlargement (e.g. 1 : 9, 1 : 14, 1 : 16—cf. the normal, *ca.* 1 : 50) was encountered in all cases of endothelioma excepting one case of lymphangiogenous endothelioma of the dog. As it was, however, also seen in some of the tumours diagnosed as lymphangioma, it cannot be considered as of vital significance in the assessment of those tumours according to the classificatory criteria which have here been used.

Regarding the species occurrence of lymphangiogenous neoplasms, it should be mentioned that previous records of lymphangioma and lymphangiogenous endothelioma in the bovine and of lymphangioma in the mule, which are here reported, have not been found in the available literature.

CHAPTER IX.

Short Notes on Glioma; and on Tumours of Melanin-pigmented Cells, of Muscle, of the Adrenal, and of the Precursors of the Blood Cells.(¹)

A NOTE ON GLIOMAS IN DOMESTICATED ANIMALS WITH SPECIAL REFERENCE TO BIRDS.

IN the earlier literature on neoplasms of animals few acceptable reports of glioma occur. In Joest's textbook (II, p. 591) we read that such tumours have been recorded in the dog—in the cerebrum by Marchand, Petit, and Pécard (1907), in the spinal cord by Piana (1889) and in the Gasserian ganglion by Gratia (1889); and in the bovine by Joest himself—in the cauda equina and in the retina (gliosarcoma). Fox (1912-13) reported as a glioma a lesion of the brain of a parakeet but this case was not acceptable to Joest and Ernesti (1917) chiefly because neuroglia fibrils were not demonstrated and there were metastases to the liver (glioma and gliosarcoma being considered non-metastasizing neoplasms). Nor was an early case of supposed glioma in a bovine reported by Dorrwächter (1896) acceptable to Casper in his review of the same year; he considered the neoplasm to be more probably a (polymorphic celled) sarcoma of the spinal meninges. More recently Dawes (1930) has reported a glioma of the brain of a dog; this tumour was considered to be an ependymal glioma, but photomicrographs are not published. Schlotthauer and Kernohan (1935) have published a full histological account of a canine cerebral glioma considered to be a *spongioblastoma multiforme*. No reports of glioma in the domesticated birds occur, and apart from Fox's doubtful case, these tumours have not to my knowledge been observed in any avian.

It is of interest, therefore, to record two cases of domestic fowls which were affected by brain tumours, in one of which the gliomatous nature was proved. In the other tumour, unfortunately, although haemalum-eosin stained sections remain, the specimen was destroyed. From the similarity of its morphology to the proved glioma, however, I was completely satisfied that this second case is also a glioma.

(¹) It is scarcely necessary to say that the various tumours which form the title of this chapter are not grouped together for anything more than convenience of presentation. These neoplasms are either represented in the collection by too few examples or by material not specially suited for the undertaking of a lengthy study of each type.

Case 1 (*Fowl*, 14258).

The subject was a Light Sussex hen, about one year of age which was reported(²) never to have laid, to have run veering to the left, and often to have fallen over on its left side. Finally the bird was unable to stand, lay on its left side and although it continued eat and drink it appeared stupified. *Neurolymphomatosis gallinarum* was suspected. The specimen as seen by me consists of a transverse section of the brain (*ca.* ·5 cm. in thickness) the anterior face of which transects the posterior part of the cerebrum, 3 to 4 mm. oral to the transverse fissure and the posterior face of which transects the optic lobes. On both the oral and the aboral aspects of this slice of brain are seen foci which contrast with the surrounding brain tissue on account of their distinctly whiter colour. In the unfixed specimen they were also softer in consistence than the normal tissue. They vary a good deal in degree of circumscription but none appears to be encapsulated. In the following description it is assumed that certain of the foci as they are seen in this slice of brain when its aboral aspect is examined are continuations of foci present on the oral aspect; but it was not desired to destroy the specimen for the sake of actually proving this by the cutting of serial sections. The foci may be described as follows:—

Oral aspect of the section.—(*a*) A rather sharply outlined quadrilateral focus, 8 by 9 mm. which stands vertically on one of its angles. It is situated mainly in the lower part of the mesostriatum of the left side, but it deflects the septum considerably to the right and also continues through the latter to occupy a small part of the ventro-medial portion of the right mesostriatum adjacent to the tractus septo-mesencaphalicus. Its upper angle protrudes into the left lateral ventricle. (*b*) This focus is smaller and more poorly outlined. In section it also appears somewhat quadrilateral and measures 3 × 2 mm. It is situated in the lateral part of the hyperstriatum of the left side.

Aboral aspect of the section:—(*c*) An oval focus occupies the more dorsal portion of the left optic lobe. Its long axis lies more or less horizontally and it measures 9 × 6 mm. Its dorso-medial extremity abuts on the median plane dorsally and its ventro-lateral pole has replaced the dorsal portion of the tectum. This focus apparently represents the aboral extremity of focus (*b*). (*d*) A small focus, oval in outline and 4 mm. in long diameter, occupies the ventro-medial portion of the right optic lobe, abutting on the median plane. This apparently represents the aboral pole of that portion of focus (*a*) which extends over to the right side. (*e*) A minute focus, poorly outlined and 1 mm. in diameter, lies in the right optic lobe immediately ventral to the dorsal extremity of the tectum.

It thus appears that there were altogether three tumours: the two larger of these stretched from the corpus striatum in front into the optic lobe behind, one being confined to the left side and the other being situated mainly on the left side but extending also across to the right side. The third tumour was much smaller and was situated in the optic lobe of the right side.

(²) Mr. D. Coles, B.V.Sc., kindly supplied the history.

Microscopically (Figs. 150, 151, 152), the tumour foci are unencapsulated (Fig. 150). Their parenchyma has some tendency to be divided into lobules of rounded outline and irregular size and often showing a more open or lace-like texture of their central portions. This is due to the presence of a stroma which consists chiefly of blood-vessels, accompanied by a small amount of connective tissue; this vascular stroma is enhanced in prominence by adventitial accumulations of small lymphocytes. The parenchyma consists of more loosely packed or sometimes more closely aggregated cells which

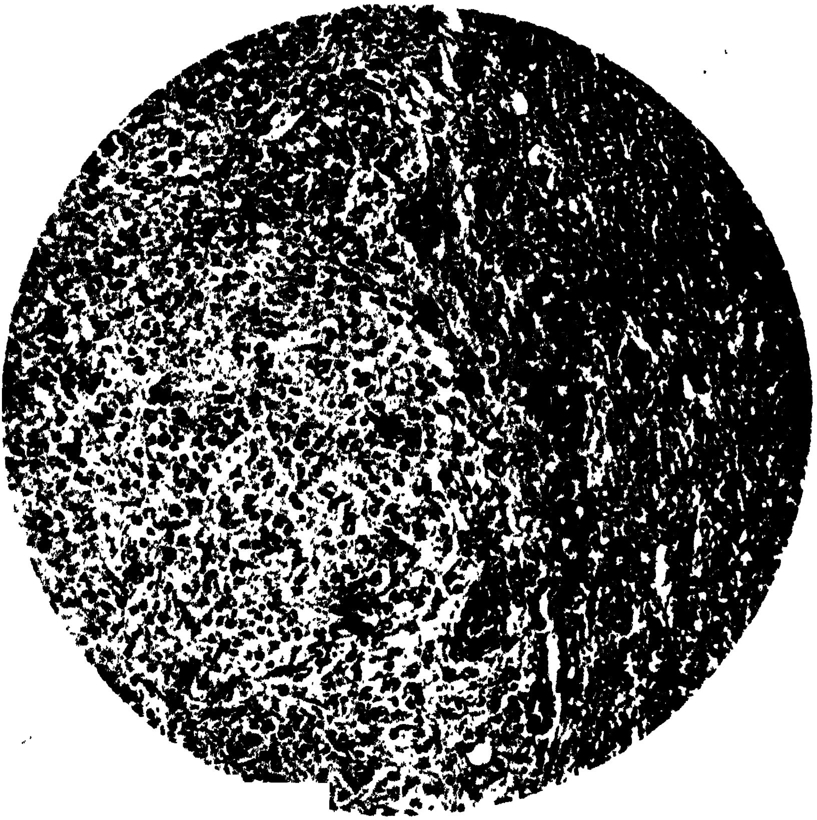

FIG. 150.—Glioma of the cerebrum of the fowl: Encroachment on the brain substance (right). 14258; 240 ×).

are characterised by pale, oval, distinctly vesicular nuclei and a cytoplasm which has many fibril-like prolongations, conferring a distinctly stellate appearance on the cells (Fig. 151). Especially where the cells are more loosely arranged, the cytoplasmic processes are seen to form an intricate, much tangled, and irregular feltwork (Figs. 151, 152). Scattered amongst these cells are isolated (infiltrating) round cells, similar to those situated perivascularly in the stroma.

The tumour cells may have no definite arrangement, or in parts may be arranged with their longest diameters parallel. Van Gieson staining demonstrates the absence of collagen from the parenchyma; with either of Mallory's fibrillar stains, however, one sees a tangled and all-pervading feltwork of fibrils reacting for neuroglia (deep blue with the phosphotungstic acid haematoxylin stain—Fig. 152) and which at their origins are so intimately associated with the protoplasmic prolongations of the cells that they appear to branch off from or to be direct continuations of the latter. The nuclei are, on the whole, of fairly uniform appearance, varying usually from 6μ to 8μ in long diameter, and have inconspicuous nucleoli. In places moderately hyperchromatic nuclei may be found and these are usually larger, up to 15μ in long diameter, and may have somewhat more conspicuous nucleoli; the n : N ratio, however, does not exceed 1 : 32 in any cell and in the majority it is more in the neighbourhood of 1 : 80. Mitoses are not seen.

Remarks.—The site of occurrence, macroscopic appearance and the histology, notably the microchemical demonstration of neuroglia fibrils connected with the cells and the absence of collagenous fibrils from the parenchyma place the assessment of this neoplasm beyond doubt. In histological type the tumour would appear to correspond most closely with the *spongioblastoma multiforme* of man, according to the classification of Bailey (1927).

Diagnosis.—(Multiple) glioma of the cerebrum.

Case 2 (*Fowl*, 9805).

It is not possible to give an accurate account of this specimen, which was unfortunately destroyed by error before the examination had been completed. Only stained sections of the brain remain for examination and it is consequently not possible to apply special staining methods to the brain lesions. The specimen consisted of the brain of a fowl, showing foci in the cerebellum; and the liver, also showing foci.

Microscopically, a section of the cerebellum discloses the presence of invading foci of a tissue closely similar to that described in Case 1. A somewhat lobulated structure is conferred by septa of delicate connective tissue, carrying small blood-vessels which show perivascular accumulations of round cells (lymphocytes and plasma cells). Enclosed by these septa are solid aggregations of cells having irregular shape and disorderly arrangement. Their cytoplasm is rather large in amount and usually faintly acidophilic—dull pink, but at times also a dull mauve, with haemalum-eosin. It is prolonged into prominent processes. The nuclei are short-oval in shape and vesicular in type. Most vary in long diameter from 7μ to 12μ. They have a very rarefied chromatin network and usually one inconspicuous nucleolus is seen (the n : N ratio being usually *ca.* 1 : 100); although occasionally larger nucleoli occur and the n : N ratio may reach 1 : 14. Sometimes a single cytoplasmic mass is provided with several nuclei. Mitotic figures can be found, although they are rare.

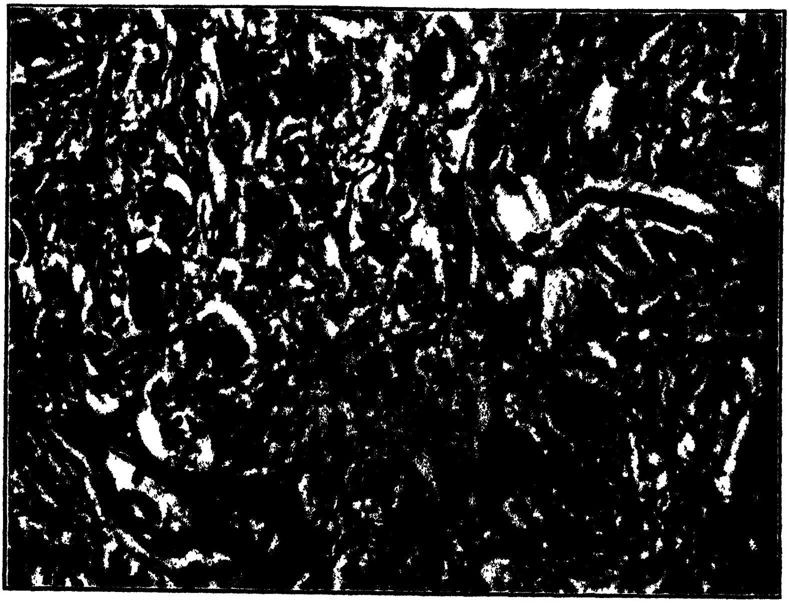

FIG. 151.—Structure of the glioma shown in fig. 150: Intimate continuity of neoplastic spongioblasts with fibrillar prolongations of their cytoplasm. (14258; 500 ×).

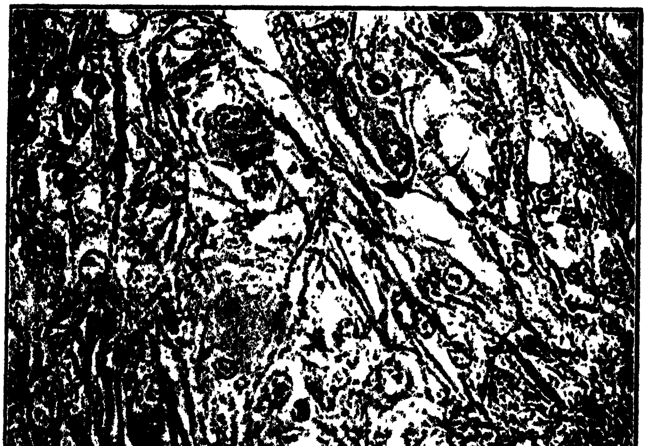

FIG. 152.—Specific reaction of the glia fibrils in glioma of the fowl (figs. 150 and 151) to Mallory's phosphotungstic acid haematoxylin staining. (14258; 625 ×).

Delicate secondary septa, composed almost entirely of blood-vessels with mantles of round cells, indistinctly subdivide the larger lobules of the parenchyma. But there is otherwise no trace of collagen among the parenchymatous cells. The focus is unencapsulated.

The liver specimen was not considered satisfactory for examination. Multiple foci are present whose nature was not clear, but in which neuroglia fibrils could not be demonstrated. There was no proof that these foci were neoplastic or related to the brain lesions. It is of interest to record that in Fox's case is mentioned the presence of a " slightly atypical metastasis in the liver ". He does not, however, enlarge upon this finding.

Remarks.—Although unfortunately no brain material is available for the application of glia stains, the resemblance of the haemalum-eosin- and van Gieson-stained sections in structure to Case 1 is so marked that one is satisfied that a similar diagnosis is justified. This tumour is somewhat more anaplastic and more rapidly growing and some would doubtless term it a gliosarcoma. The difference is, however, only one of degree, and that term is not favoured in modern nomenclature.

Diagnosis.—Glioma of the cerebellum.

Summary.

Two cases of glioma of the brain of fowls are described. Such tumours, exceedingly rare in domestic animals as a whole, have not been recorded for this species and indeed no entirely satisfactory proof of their occurrence in members of the class *Aves* has yet been offered. The diagnosis has depended on the finding of non-encapsulated, softer, and whiter foci in the brain substance, which on microscopic examination are found to consist of a lobular or alveolar arrangement of stellate cells associated with the production of a feltwork of non-collagenous fibrils which react, not for reticulum, but for neuroglia. The specific fibrillar staining could, however, be applied only in one of our cases. Apparently grades of malignancy exist, as shown by variation in the presence of mitotic figures, and absence or presence of moderate nucleolar enlargement. The possibility should be borne in mind that the apparent rarity of glioma in domesticated species, especially in birds, may in part be ascribed to failure to make a thorough examination of the central nervous system in routine autopsy work. Gliomas of the human subject are nowadays being elaborately classified. It seems doubtful whether with our limited experience of gliomas of the lower animals, in all (including my own) some nine possible cases, that the time is ripe for the application of such a detailed classification to the lower animals.

A NOTE ON THE MELANIN-PIGMENTED NEOPLASMS.

Much confusion surrounds the problem of the histogenesis and classification of melanin-pigmented tumours and in spite of the large literature which surrounds this subject we cannot reach final conclusions until we know accurately the genesis of cells carrying melanin pigment and the metabolism of melanin in the body. Comparative pathology has important material to contribute to this study, for melanotic neoplasms are common in several species of domestic animals and are known in practically all. Two types of domestic animals are especially frequently the subjects of melanotic tumours, viz. grey horses, in which the incidence is such as allows one almost to predict that every such animal which lives long enough is fated to develop these tumours; and the Angora goat, the high incidence of melanotic tumours in which has been disclosed by the work of Thomas (1929) in this country. The term melanoma, applied to tumours of which the cells are melanophorous, is of course a confession of ignorance and it is probable that under this category are included tumours of different histogenesis and certainly composed of dissimilar cells which have little in common beyond their content of melanin; when we reflect that in these cases we are largely ignorant of whether the pigment is being produced by the cells or merely taken up by them, it will be seen that we are here following the undesirable principle of naming tumours by secondary or incidental features of their pathology (much as one might, ill-advisedly, group together all tumours the cells of which contain fat globules, a feature which might owe its origin to very different causes in different cases).

It has long been known that of the melanomas some are composed of cells which have an epithelial-like morphology and habitus, while others are composed of cells which in these respects resemble more the derivatives of the mesenchyme. This phenomenon has been correlated with the occurrence of melanin-pigmented cells among epithelia and in the underlying connective tissue. The tumours referred to have therefore been termed melanocarcinomas and melanosarcomas respectively, although there are those who believe that the melanotic cells to be found in epithelia (e.g. in the *stratum basale* of the epidermis) are not equivalent to their non-pigmented neighbours (the basal cells), but have come into that layer of cells secondarily. Whether or not the occurrence of melanotic cells of similar morphology to the basal epithelials among which they lie and the occurrence of melanotic tumours which in architecture and cytology present similarities to epithelial tumours is accepted as proof that epithelial cells can manufacture melanin, the finding of various grades of pigmentation among tumours like acanthomas, known beyond question to be of ectodermal derivation, shows that tumours cannot be accurately discriminated on the mere basis of melanin content of the cells. In animals pigmented acanthomas have been recorded by McFadyean (1890) for the horse, and in this work such a tumour has also been described (Equine, 15312—see Chapter II); McGowan (1928) has recorded melanotic tumours of the fowl, one of which was considered to be epithelial in nature (arising from the *membrana granulosa* of the Graafian follicle) and others of which were of sarcomatous nature; in swine melanotic tumours, which were considered to be melano-epitheliomas arising from the *stratum basale* of the epidermis and in which an alveolar arrangement of the cells was present, have been described by Caylor and Schlotthauer (1926); in the goat the occurrence of tumours considered to be melanotic epitheliomas and which apparently are very similar in morphology to those mentioned in the pig have been carefully studied by Thomas (1929). These tumours were considered by him to represent pigmented baso-cellular carcinomas; but although their epithelial nature is apparent, the propriety of this terminology is open to doubt. It will be seen, therefore, that pigmented tumours of epitheliomatous nature—in contrast with those of sarcomatous nature (and which are found most frequently in the horse)—occur in most species of domesticated animals; and that in consequence, in the words of McGowan " two types of melanomata—mesoblastic and epithelial—occur ". In these epithelial or apparently epithelial neoplasms, not only cells of epithelial nature bear pigment; as is well known, there occurs in the stroma a second type of cell—the " melanophore " as opposed to the " melanoblast "—of mesenchymal nature, corresponding with the cells of melanotic sarcomas, but in this case not neoplastic. The fact that the melanotic cells which have been grown in tissue culture by Grand, Chambers, and Cameron (1935) showed only mesenchymal-derivative characteristics does not help us in this problem, because these observers were dealing with cultures of melanotic sarcoma and it still remains possible that, could the cells of melanotic carcinomas be grown in culture—a procedure which could not be accomplished by Caylor and Schlotthauer (1926)—further proof of the epithelial nature of the cells of this class of pigmented tumour might be forthcoming.

The Onderstepoort material has not been of a nature to favour elucidation of these problems of melanotic tumours and melanin-metabolism, except in the case of the caprine specimens, which have already been reported on by Thomas. Other observers, with far more material, have been and are in a better position to take up this study in the remaining species of animals (see the recent review of McFadyean, 1933, on equine melanomatosis). We are here concerned with the pigmented tumours only in so far as to indicate their occurrence in South Africa and the difficulties of classification which exist.

The occurrence of a large number of cases of equine melanoma (melanosarcoma) in the collection is of little further interest here. The appearance of these tumours in an equine population is well known to be dependent on the proportion of grey animals, although the tumours are not strictly confined to animals of that colour. A large numbers of cases of these melanotic skin tumours are not submitted as specimens, because not only is the diagnosis obvious, but little further information than is already known can be gained by straightforward study of these tumour cells, whose character is largely concealed by their most excessive pigment-content. Among the other species, melanotic tumours occurred most frequently in the goat (40 per cent. of all caprine neoplasms). It is of interest to note that these melanotic epitheliomas of the goat are not confined to the Angoras, but also occasionally occur in other varieties (e.g. the Swiss milch type); they have not however been encountered in other than white goats. In the dog we have encountered five cases and in the pig two. A melanotic tumour of the cat was found on microscopic examination to be a basal-cell epithelioma and is described under that heading (Feline, 14021). As has been mentioned, a pigmented acanthoma was also found in the horse (Equine, 15312), as well as pigmented epithelioma without specific tendencies. Both these tumours affected the conjunctiva. The canine tumours had much the same morphology as the human melanotic skin tumours, ranging from " naevi " to definitely anaplastic neoplasms. Although groups of cells occur fairly well demarcated by the connective-tissue stroma and as a rule connective-tissue fibrils do not pass between the individual cells, these neoplasms have not a definitely alveolar or epithelial architecture and they do not fall readily under either of the types, melanotic carcinoma or melanotic sarcoma. In the cases in pigs, much the same applied; and apparently neoplasms of the epitheliomatoid type encountered by Caylor and Schlotthauer, in Duroc Jerseys only, are not represented among our material.

For the study of what are usually regarded as typical melanotic epitheliomas, however, the caprine material presents an unrivalled wealth of specimens. These tumours, as has been described by Thomas, are so strikingly epithelial in nature that one is tempted to classify them with the epithelial neoplasms, as has been done in the case of the pigmented epitheliomas from the horse and the cat. Yet it is possible that the last word has not been said regarding their epidermal derivation and one would prefer to await the final results of the theory which refers the origin of melanotic tumours to the tactile end-organs of the skin before committing oneself in this respect. In favour of their epidermal origin are the following facts: their occurrence in a variety of animals in which neoplastic proliferation of the epidermal cells and their derivatives (acanthomas, sebaceous neoplastic processes) are equally common, and at the same sites of predilection (head, ears, perineum); the occurrence in such close association with acanthomas as to lead to " collisions " of the two neoplastic tissues, producing a type of mixed tumour: (this question has been discussed by Thomas and is also referred to in more detail in the discussion of the mixed neoplasms in Chapter X); the occurrence of early lymph-borne metastases; the actual architecture of the tumour, especially the alveolar arrangement of the cells (clearly demarcated from the connective tissue and lying in solid groups or continuous strands); and the actual cell morphology, closely resembling epithelium of epidermal derivation and showing anaplastic changes closely similar to those which one may encounter in acanthomas. My views on the questionable desirability of classing these tumours as basal-cell carcinomas have already been mentioned (see Chapter II). Ignorant as we may be of the histogenesis of the basal-cell tumours we nevertheless understand by that term a very definite clinical and pathological entity, characterised by a limited invasive capacity, by absence of metastasis(3), by columnar-shaped cells of very uniform morphology, by lack of anaplastic cellular and nuclear changes, and usually by absence of formed products, e.g. pigment, from the cytoplasm. From such tumours it would seem imperative, on clinical grounds alone, to separate the readily-metastasizing and infiltrating caprine tumours, which are further

(3) There are those who, in my opinion with much justification, hold that the fact of metastasis in a tumour at once precludes its claim to be considered as a basal-cell epithelioma. Reports of metastasizing " basal-cell carcinomas " have been found, on analysis, to concern tumours transitional between acanthomas and basal-cell carcinomas, and acanthomatous characters are likely to be pronounced in the secondary lesions especially. The literature on this question is to be found in the publications of Darrier and Ferrand (1922), Montgomery (1918), and Niles (1931).

distinguished by their pigmentation, high degree of cellular anaplasia, and a very different cell morphology. It is not too much to say that between the basal-cell tumours and the pigmented caprine tumours there is nothing in common beyond their occurrence in the skin and our ignorance of their exact genesis.

It is hoped, in co-operation with Dr. A. D. Thomas to undertake further investigation of these caprine tumours at a later date. Meanwhile I have indicated some of the problems that have to be faced in the classification of the pigmented tumours for the purposes of the Onderstepoort type-collection.

Tumours of Muscle.

Rhabdomyomata are not represented in the Onderstepoort collection.

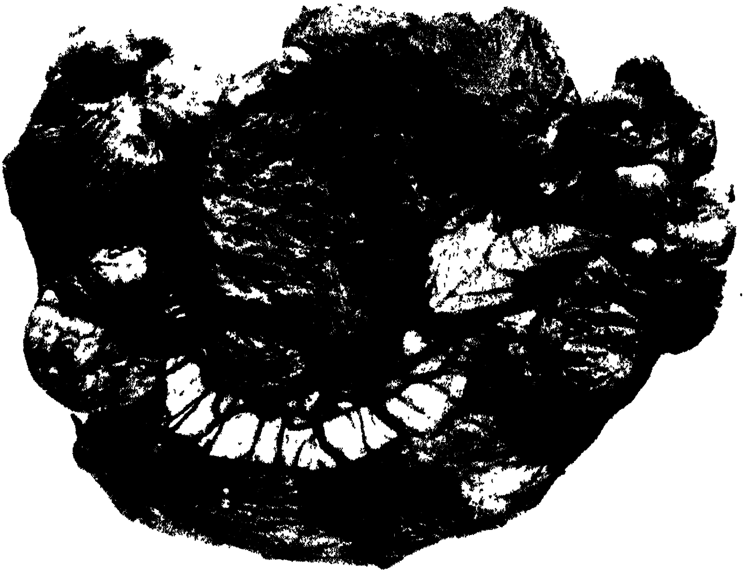

Fig. 153.—Leimyoma of the oviducal ligament of the hen: The myoid nature of the neoplastic tissue is obvious to the naked-eye. (14706; 2/3 ×.) Reproduced through the courtesy of the Editor of *Farming in South Africa.*

The great majority of leiomyomata occurred in fowls, in which the common occurrence of these tumours is well known. The most usual site is the ligament of the oviduct (Fig. 153) or the oviduct (often the uterine portion) itself (14 cases). In one case the ovary (see Fig. 154), ovarian bursa, and proctodeum were affected by multiple *leimyoma fibrosum* ("fibromyoma"). This ovarian "fibroid" was very large, weighing approximately 2 lb; in another, both ovary and oviducal ligament were involved by a leiomyoma. In a large proportion of leiomyomata the blood-vessels of the stroma are very prominent (*leiomyoma haemangiomatosum*): these tumours were not

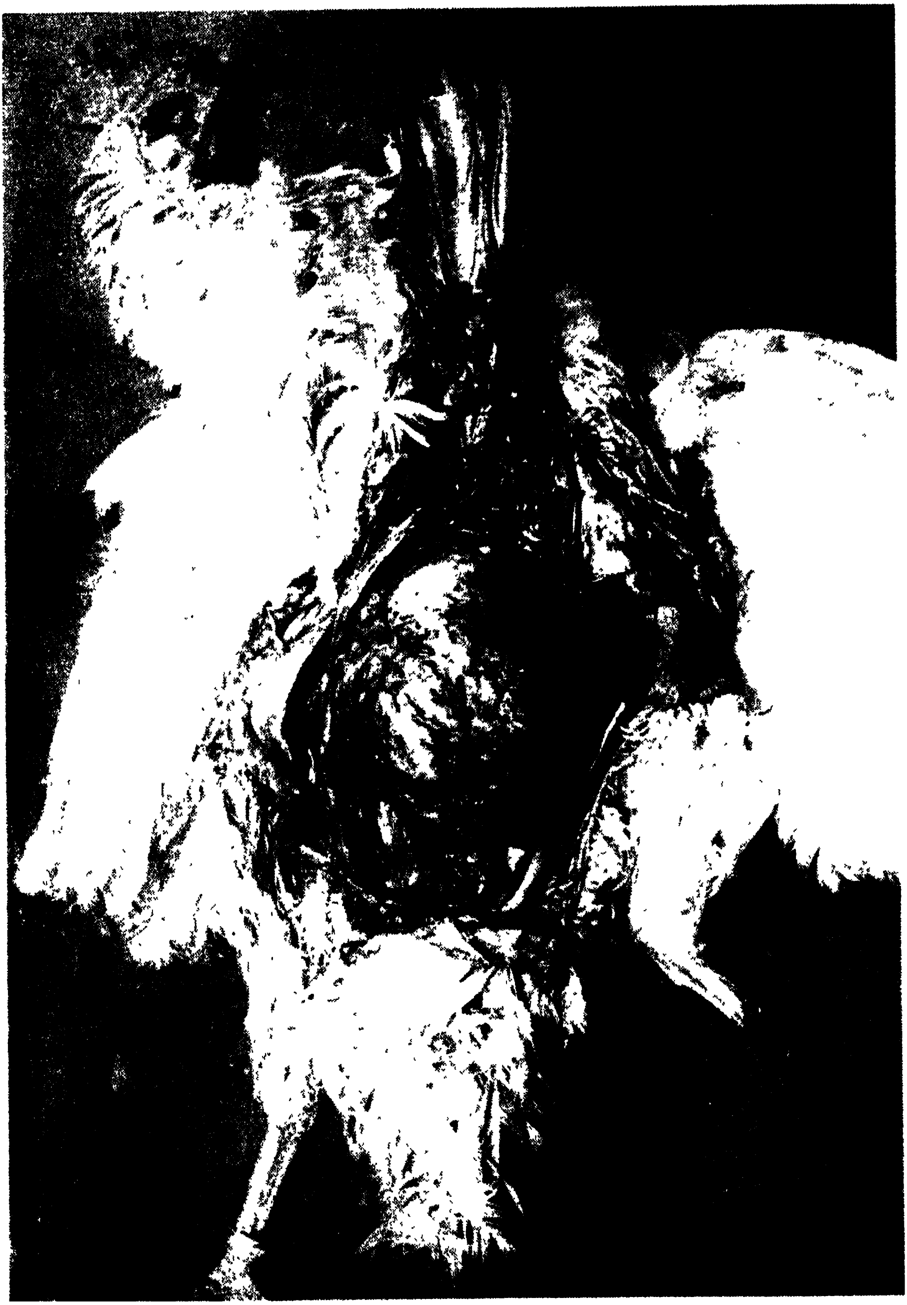

FIG. 154.—A large *leiomyoma fibrosum* ("fibroid") of the ovary of a hen. The tumour weighed about 2 lb. (Reproduced through the courtesy of the Editor of *Farming in South Africa*).

considered to be mixed neoplasms (haemangioleiomyomata), and all gradations in vascularity exist to the ordinary leiomyomas. As has been discussed when dealing with the epithelial tumours of the avian genitalia and as will be mentioned again in Chapter X, a leiomyoma-like moiety accompanies many adenoid carcinomas (*carcinoma leiomyomatosum*) and we were not inclined to consider these as mixed neoplasms; further, it was also pointed out that not every neoplasm composed of smooth muscle can be regarded as a leiomyoma in the fowl: such nodules may be implantation metastases of a *carcinoma leiomyomatosum* in which, accompanied by great proliferation of the muscular stroma, the epithelial elements have undergone regression. The total number of leiomyomas encountered in fowls was 14. On the other hand only two smooth muscle tumours were found in mammals; multiple leiomyomata of the urinary bladder of a goat (14142) and a malignant leiomyoma ("leiomyosarcoma") of the vagina of a bitch (Canine, 16310).

The structure of tumours of muscle is well known and details will not be entered into in this text.

A Note on Tumours of the Adrenal Gland.

Tumours of the adrenal have long presented a problem in classification to which the somewhat limited material in the Onderstepoort collection cannot be expected to furnish any final solution. These tumours have long been treated as a group apart, recognised under the name of hypernephroma. In recent years there has been an increasing tendency to restrict this term to tumours of the adrenal cortical elements, those arising from the elements of the medulla being termed phaeochromocytomata or neuroblastomata, etc., according to their nature and that of the stage which has been reached in the differentiation of the neuro-ectodermal elements from which they arise. It has also become customary to attempt a division of the (cortical) hypernephromas into benign and malignant types: some authors (e.g. Geschickter, 1935) identify these with adenomas and carcinomas respectively. There is, however, at least to the student of comparative histology and oncology, a grave objection to this terminology, because it carries with it an admission of the epithelial nature of the cortical elements and of the neoplasms derived therefrom. But the fact is that these peculiar cells, of mesodermal derivation, are by no means clearly of such a nature, and it is well-known that, in domestic animals at least, intercellular fibrils are demonstrable in the adrenal cortex, a circumstance which, strictly speaking, is inconsistent with the epithelial nature of these cells (see Chapter II). Even if, for the purposes of normal histology, one is, on account of the not very obvious nature of these reticulum fibrils, willing to overlook this incompatability, in comparative oncology one is soon confronted with the difficulty of tumours, clearly of cortical origin, of which the cells are quite clearly related to fibroblastic elements rather than to epithelium. This dual potentiality of the cortical elements was long ago recognised by Adami (1910) and by Woolley (1902), who therefore spoke of cortical tumours as "mesotheliomas". The latter author showed that an apparent adrenal "carcinoma" may have sarcomatous metastases. This being the case, we should not be willing as yet to follow the more recently urged nomenclature of tumour pathology and should rather, for the time being, be content to place these neoplasms in a separate category, practical difficulties being overcome by speaking simply of benign or malignant (cortical) hypernephromata, as the case may be.

In the assessment of localised enlargements of the suprarenal arise difficulties in distinguishing between congenital anomalies or displacements, localised hyperplasias, and benign and malignant tumours which are in many respects comparable to those with which the study of hepatic and thyroid neoplasms has made us familiar (Chapter IV). Here again, there is little doubt that a strict separation of such processes may, in atypical or intermediate cases, result in an artificial classification. Yet, so far as is possible, the attempt has to be made.

Lesions considered to be accessory cortical nodules (more frequently in the literature actually described as tumours) as well as localised hyperplasias have not been included in the statistics. Accessory nodules of cortical tissue, usually described as lying within the adrenal capsule or without the adrenal, may also occur within the cortex or even in the medulla of the gland. Many of such nodules, if serial sections be cut, can clearly be seen to have arisen as invaginations of the cortex, and these consist of a central core of connective tissue (representing the capsule) which is surrounded in turn by the various layers of the cortex, the reticularis (now the outermost) being circumscribed but not encapsulated from the normal cortex or medulla (as the case may be) into which the invagination has occurred (Fig. 155). Other of these nodules are very similar in structure, but do not have their layers inverted and are therefore demarcated peripherally by a capsule. Their existence might be explained as a growth of other cortical elements around the area which comes to form the nodule, or as a displacement of less differentiated cells into the deeper layers, in other words the result of nothing more than a mistiming or lack of synchronization of growth- or differentiation-rates in various parts of the developing organ. There is nothing in either of these types of lesions, save their naked-eye appearances, to suggest a neoplastic process: they lack the usually accepted criteria of true tumours; in minute structure there is no departure from the normal and the surrounding tissues do not betray evidence of growth pressure. It is not desirable, therefore, to identity these nodules with neoplasms, the more so since there do exist enlargements of adrenal cortical type to which the term adenoma may, quite fittingly, be applied. Localised hyperplasias of the cortical tissue are also to be distinguished from tumours: typically they lack encapsulation, do not exert a growth pressure on their surroundings, often occur in multiple form, and structurally do not depart significantly from the normal; in other words they lack the characteristics of autonomous growths and are the reflection (cf. the liver and thyroid tissue) of an inherent propensity for a vigorous repair of damage which the cortex may suffer. There are however intergrades (again compare the liver and the thyroid) in which discrimination from neoplasms may be somewhat artificial.

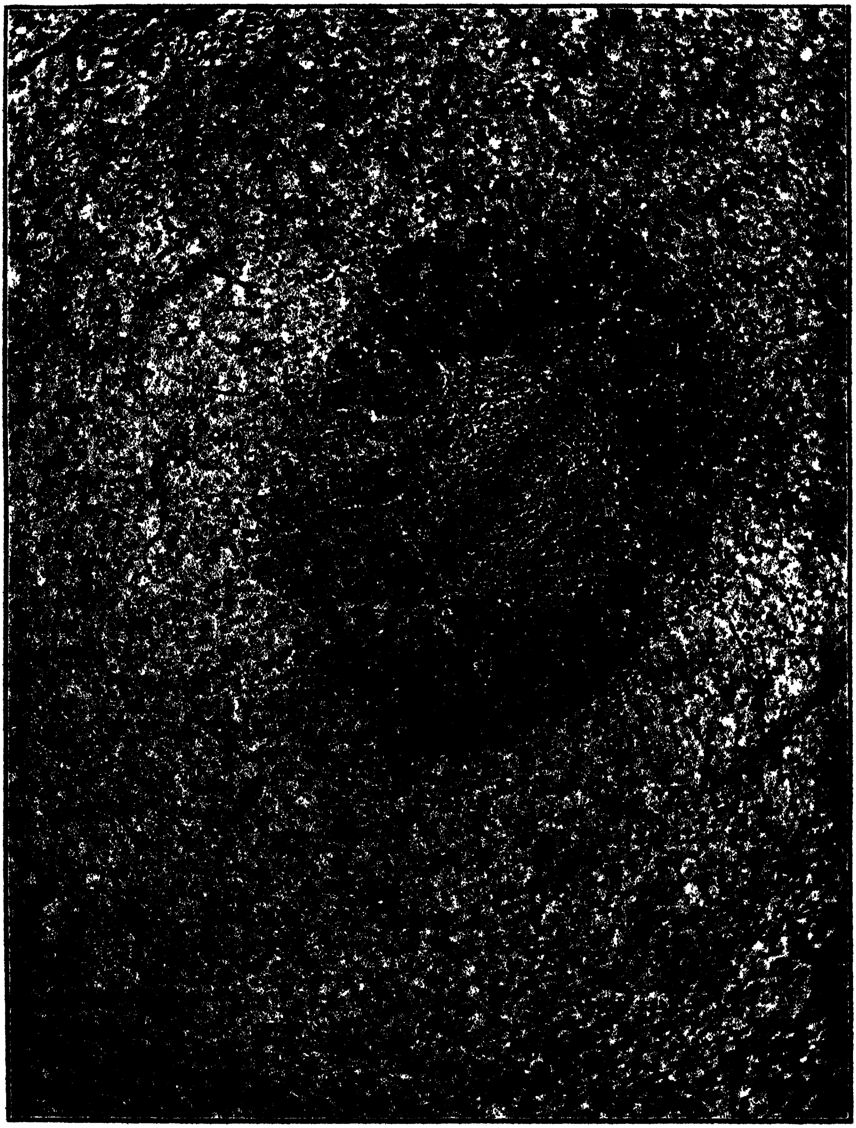

Fig. 155.—A nodule consisting of an invagination of cortical tissue in the adrenal medulla of a goat: The order of the cortical layers in the focus is reversed, i.e. centrally a core of connective tissue (capsule) then an indistinct *zona arcuata*, while the bulk is constituted by a *z. reticulata* which (left top corner and right bottom corner) abuts on the medullary tissue of the gland. (15755; 110 ×).

After elimination of lesions of the two above-mentioned types from our hypernephromata, the Onderstepoort collection contains only ten examples of true adrenal tumours. These readily fall into the accepted classification:—

1. (*Cortical*) *Hypernephromas.*

Of eight cortical tumours, six are regarded as benign and two as malignant.

(*a*) *Benign Tumours.*—Two of these occurred in horses, two in sheep [a species in which the occurrence of adrenal tumours has for the first time (as lately as 1931) been mentioned by Feldman] and two in oxen. All these tumours were encapsulated nodules, causing compression of the surrounding tissue. One bovine tumour (5925) bore much resemblance to the first equine case to be mentioned, being of the *zona reticularis* type and showing an almost identical "hernia" through the capsule at one point. One of the equine tumours (12575) was characterised by an excessive lipoid content of the cells which, apart from a resulting mechanical compression of their nuclei, showed no significant differences from the normal elements of the *zona reticularis*. At one point the capsule was deficient, and what might be described as a small hernia of the neoplastic tissue protruded into the adjacent cortex; it lacked signs of invasive growth, however, and did not lead one to doubt the benign nature of the tumour. In the other equine case (5570) both the *zona reticularis* and the *zona fasciculata* were imitated in different parts of the tumour. In the ovine cases (10054 and 13867) the cells were almost exclusively of spindle shape (Fig. 156) and one could

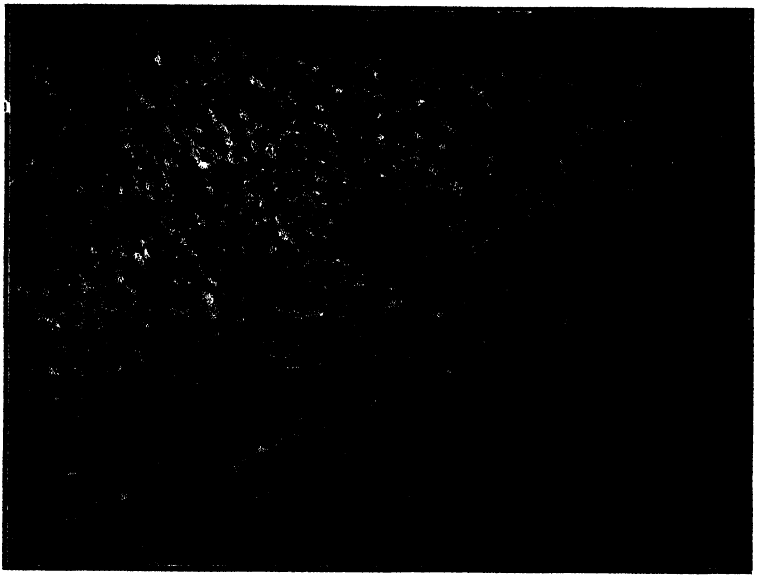

FIG. 156.—Structure of a spindle-celled cortical hypernephroma of the adrenal of the sheep. (13867; 180 ×).

not here speak of "adenoma" without conveying a misleading picture of the histology. The cells of these sheep tumours are clearly closely allied to fibroblasts and show little if any epithelial characters. Although there is considerable variation of nuclear size, other signs of anaplasia are lacking and the mitotic index is nil, so that there is little justification for misinterpreting them as sarcomas. Occasional cells show the presence of intranuclear inclusions of the type considered to be derived from nucleoli, otherwise the nucleoli are not enlarged. There are no signs of invasive growth. In the one case, however, encapsulation failed at part of the circumference and here the neoplastic tissue blended gradually with the normal, reminding one of a hyperplasia rather than a tumour. Both neoplasm and adrenal tissue are infiltrated by eosinophiles. These lesions have characters that remind one of embryonal types of tumours (cf. those of the breast and the "foetal" adenoma of the thyroid). One feels, in view of this and of the presence of nuclear "inclusions", that the possibility that these tumours may be in an incipiently malignant stage and might have progressed to malignancy in course of time must be borne in mind. On the other hand, the peculiar nature of these lesions with their superficially sarcomatous appearance, lack of anaplasia (except for disorderly arrangement of the cells), and eosinophilic infiltration tempt one to point out their similarity in all these respects to the contagious equine sarcoids (see Chapter X). The possible significance of such an obscure relationship will not, however, be pursued here any further.

(*b*) *Malignant Tumours.*—Malignant (cortical) hypernephromas were found in one bovine and one equine. The case in the horse (12614) was accompanied by metastasis to the mesenteric lymph-nodes, and the wall of the vena cava (lymphatics of the adventitia) was also invaded. The cells were of a single type, apparently epithelial in character, bore no resemblance to the medullary elements, and were arranged in thick solid cords separated by a delicate capillary stroma with little collagen. The mitotic index was high. The bovine case (15650) was, histologically, a (false or embryonal) mixed tumour, which is conceived as being derived from the corticogenic mesoderm: it consists of both epithelial-like elements of the cortical type and fibroblastic elements, as well as transitional forms and endothelioid cells (see Fig. 157). An interesting feature of this tumour is the simulation by some of the outlying alveoli of the neoplastic parenchyma, of a *zona glomerulosa*, a structure which is absent from the normal adrenal cortex in the ruminant.

2. *Phaeochromocytoma.*

Two certain cases of these tumours occurred—in a bovine (8262) and an equine (13449) respectively. The equine case was easily recognisable as a (clinically) benign tumour composed of neoplastic phaeochromocytes. As Rabin (1929) has pointed out, the cellular anaplasia to be found in these tumours as well as the occurrence of numerous blood-channels lined directly by neoplastic cells are not to be regarded as signs of malignancy. He refers these features to a natural growth-mode of the cells. In the bovine case similar circulatory channels were present, but contained more lymph than blood. In a third case (in a bovine, 4196) the diagnosis of phaeochromocytoma remains a mere probability: calcific changes ("psammoma") have overtaken the greater part of the tissue available for examination, which has also suffered changes from long preservation (over 11 years).

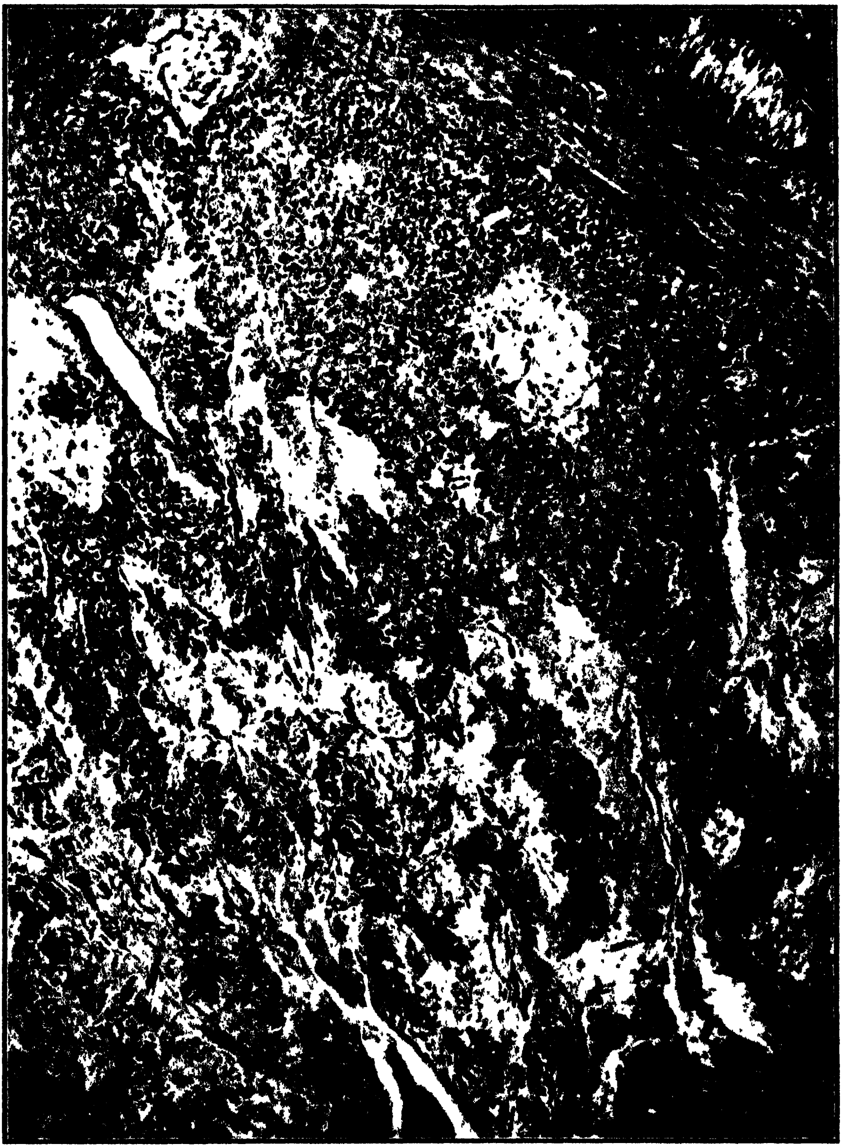

FIG. 157.—Embryonal cortical hypernephroma of the ox: Growth largely of a sarcomatous type; above, right, the tumour capsule which is invaded by neoplastic tissue simulating a *zona glomerulosa*. (5576; 60 ×).

A NOTE ON TUMOURS COMPOSED OF THE ELEMENTS OF THE LYMPHOID TISSUE, AND ON TUMOURS AND NEOPLASTIC DISEASES IN WHICH THE PRECURSORS OF THE BLOOD CELLS PARTICIPATE.

A. *The Fowl.*

In the bird, the classification of neoplastic proliferative processes involving the blood-forming elements presents serious difficulties, for the following reasons:—

1. All gradations occur between more or less discrete neoplastic enlargements of this type and more diffuse affections of the organs and tissues in which one cannot speak of primary growth and secondaries or in which no actual tumour is formed. Yet these different appearances obviously are closely related and it is not possible, except in the extreme cases, satisfactorily to differentiate between neoplasms and " leucoses ".

2. From the aetiological standpoint there is as yet no agreement as to the relationship between the three varieties of neoplastic proliferative processes in which different blood-cell lineages are concerned. To-day the weight of evidence is in favour of the non-transmissibility of lymphoid leucosis (Furth, 1931a, Feldman and Olson, 1934), and of the transmissibility plus interchangeability of myeloid and erythro-leucosis. There are, however, still several authorities who believe that lymphoid as well as the other two forms of leucosis is transmissible by cell-free filtrates (Ellerman, 1921), and others who believe that interchangeability of leucoses with sarcoma of the Rous type (Furth and Stubbs, 1934), and even with lesions called " endothelioma " may be demonstrated (Furth, 1934). For the present, however, we may hold, as a working plan (*a*) that lymphoid leucosis is non-transmissible and aetiologically dissimilar to erythro- and myeloid leucosis; (*b*) that the latter two are interchangeable, i.e. that with cell-free filtrates of the one type one can produce the other type of disease; (*c*) that the aetiological relationship of leucoses and sarcomata cannot be regarded as satisfactorily elucidated, but that an excellent case has been made out for further investigation. The difficulty which hampers this type of investigation and which may seem strange to those who have no experience with avian neoplastic proliferative processes, is that the extremely high " spontaneous " incidence of these diseases is such as to lead to inconclusiveness in all but the most elaborately controlled transmission experiments.

3. Although in erythroleucosis no actual tumour is formed in the body, the cell proliferation being confined to the blood-stream and the neoplastic elements being therefore and by their nature unable to cohere to produce discrete enlargements, yet the aetiological identity of this disease with myeloid leucosis and the grading of the latter from diffuse proliferations into discrete tumours (myelocytomas) makes any discussion of neoplasms which treats of " myelocytoma " but neglects myeloid leucosis a highly artificial one; similarly, it does not seem to me to be advisable to attempt a rigid distinction between " lymphosarcoma " and " lymphoid leucosis ", there being all intergrades from the cases in which one can speak of

a primary tumour and trace its metastases, to those in which multiple foci occur in many different organs, none apparently of a secondary nature.

Under these difficult circumstances, it has seemed advisable, if any mention at all is to be made of such diseases in fowls, to deal with them all. Although the Onderstepoort collection contains a large number of specimens of these cases the material has not been particularly suitable for pathological study, because blood examinations were not made at the time. It is, therefore, not proposed to do more than to give a short account of the occurrence of these conditions in South Africa.

Malignant lymphocytoma (lymphoblastoma), including lymphoid leucosis, is by far the commonest neoplastic disease of fowls in South Africa, the collection actually containing specimens of 91 cases, as well as one case in a turkey. In the majority of these cases no autopsy was performed; one simply received fragments of one or more organs preserved in formalin. The pathology of these lesions is well known: one may encounter solitary primary tumours composed of the cells known as lymphoid haemoblasts (lymphoblasts, large lymphocytes, haemocytoblasts, haemohistioblasts, lymphoid wandering cells, etc., etc., according to different authors) suspended in the meshes of a reticulum: or similar primary tumours apparently with blood-borne metastases, or organs affected by " lymphoid leucosis "—especially the liver (Fig. 158), kidney, etc. The large discrete tumours may be found affecting the skin, ovary, lung (Fig. 159), cloaca, etc. These tumours have been known under various names, in the older literature being classed as sarcomas (round-celled sarcoma, *sarcoma globocellulare*, lymphosarcoma) and most of the older statistics for the occurrence of sarcomas in fowls included these tumours with the true sarcomas (e.g. fibroplastic sarcoma, " mixed-celled " sarcoma, myxoplastic sarcoma, etc.): such figures are therefore not directly comparable with more modern ones, where there has been a very general agreement to treat of tumours of lymphoid cells as a class apart from those of connective-tissue cells. The incidence of the neoplastic disease under discussion appears to vary widely: throughout the German literature we read of its very common occurrence (cf. Joest and Ernesti, 1916, Pentimalli, 1916, Malke, 1930; also Tyzzer and Ordway, 1909), while McGowan (1928), in an extensive study of neoplasia in fowls mentions that he failed to encounter a single case. Almost all the earlier workers termed these tumours " round-celled sarcomas ". This term is to-day much out of favour, especially in the case of birds.

Myeloid leucosis and myelocytomas are, on the contrary, among the rarer diseases of fowls in this country. We have encountered only three cases, two of which existed as collision tumours with " mixed-celled " sarcoma of the ovary; one of these has been reported together with the sarcomas (Fowl, 15100) in Chapter VII. As was mentioned there, it seemed that in this case one was dealing with a myelocytoma in the narrower sense: it appeared to be primary in the ovary while the secondaries were represented by haematogenous metastases to the epicardium and by multiple implantations on the abdominal serosae. Not only the two primary tumours but

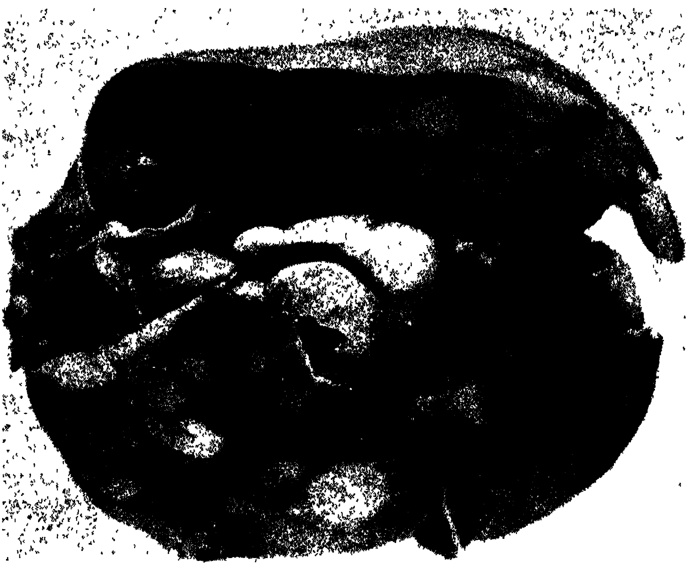

FIG. 158.—Lymphocytomatosis (lymphoid leucosis) of the liver of the fowl. (10351; natural size).

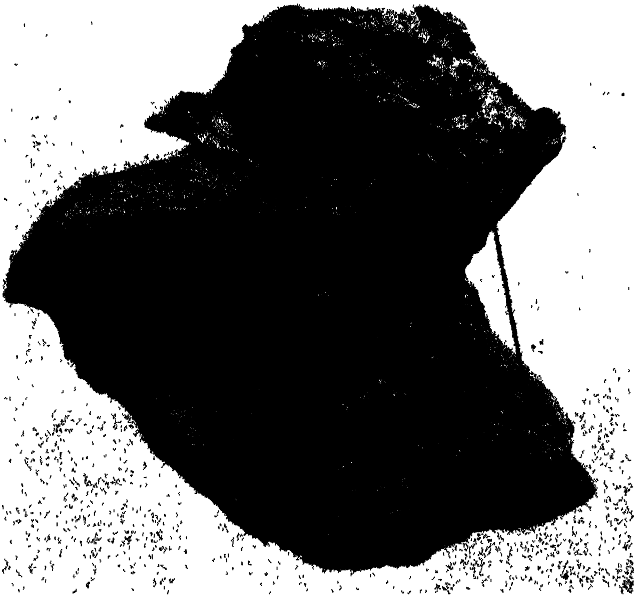

FIG. 159.—Thoracic wall of a fowl showing lymphocytoma of the lung attached to the ribs and infiltrating the musculature. (15962; 2/5 ×).

also their implantations had undergone "collisions" and intermingling of their tissues in places. Histologically, the disease in question consists of proliferations of myelocytes and there may in some cases be a myelogenous leucaemia. It is surprising that nowhere in the literature can one find a more accurate identification of the cells concerned. It seems usually to be assumed that they are the neoplastic counterparts of true eosinophile myelocytes, because their granules are usually rounded. This conception is erroneous. Actually the cells are pseudoeosinophile myelocytes, the precursors of those granulocytes of the fowl which have rod-shaped (spindle-shaped) granules. The confusion arises because of the failure to realise that in the earlier myelocytic stages the pseudoesinophilic granules are rounded, only becoming rod-shaped as the cell matures. Such rounded pseudoeosinophilic granulations can be distinguished from the true eosinophilic granulations because the former (i) are coarser, (ii) some of them are actually basophilic in reaction, developing eosinophilia at a later stage, and (iii) because on close examination a tendency can often already be seen to a slight elongation of the granules. For those who have difficulty with this conception it is essential to undertake a study of normal avian red marrow, when the above features will readily be determined; it must be borne in mind however that in the marrow true eosinophile myelocytes for comparison are often somewhat difficult to find and must be searched for. It is apparently for this very reason that those examining avian marrow and expecting readily to find precursors of both types of the granulocytes which have eosinophilic granulations, go astray by identifying as their precursors cells with round granules and cells with rod-granules respectively, both of which are in reality stages in one and the same line of descent. [The pseudoeosinophile myelocytes are also favourably to be studied in the blood of the ostrich in which they circulate in the apparently normal adult(⁴)].

Five cases of erythroleucosis have come to our notice in this country. Doubtless many more occur than is indicated by this small number, but the clinical diagnosis as well as the macroscopic diagnosis at post-mortem being by no means readily made, and no actual tumours occurring, specimens and blood smears are not often submitted to this Department.

B. *Mammals.*

In regard to this class of animals, very similar if somewhat less acute difficulties occur in the classification of the tumours we are considering, and the neoplastic nature of leucaemic diseases still remains a matter of controversy. There is to-day, however, a strong tendency to identify leucaemias as neoplasms of the circulating blood and to take cognizance of them in discussions on neoplasia. We cannot hope to arrive at a satisfactory classification of these diseases in animals, modelled on human nosology, until such time as advance of knowledge shall purge the latter of its truly dismaying confusion.

(⁴) For the opportunity to make this observation I am indebted to Mr. O. T. de Villiers, M.R.C.V.S., who asked me to identify these immature cells in the preparations of ostrich blood made by him.

LEUCOTIC TUMOURS.

Very few of these tumours have been found in this country:—Tumours composed of lymphocytes (lymphosarcomata) have been found in oxen, sheep and dogs. Lesions of this type from two sheep (Ovines, 5579 and 9196) one ox (Bovine 5124) are contained in the collection. Three of the cases in dogs, the lesions of which have been described in this country by Fourie and Ziehn (1930) as lymphoid aleucaemia, viz. a generalised lymphosarcomatosis, have been encountered. One of these cases has been fully dealt with by those authors and the others are similar in all respects to what they described. The material obtained from oxen and sheep, usually consisting of a single lymph-node or a tumour arising therefrom, is unsuitable for study except from the purely histological aspect. Autopsy and clinical records being lacking, even the diagnosis must remain vague. Neoplastic conditions involving myelocytes have not been encountered in mammals in South Africa.

CHAPTER X.

The Mixed Tumours.

A MIXED tumour may be defined as one which is composed of two or more neoplastic cellular moieties. Mixed tumours are denoted by the compound terms of oncological nomenclature; but, as has been remarked previously, such compound names have unfortunately been applied also in the case of simple tumours, in order to describe what is nothing more than a growth-mode; here a qualifying term is preferable to describe the tumours in question, e.g. " adenocarcinoma " (a simple tumour) is better called *carcinoma adenoides*, and " fibrosarcoma ", *sarcoma fibroplasticum*. Dismissing from our discussion this group of tumours which, although neither histologically nor pathogenetically mixed tumours, have been called by names suggestive of such tumours, we find that a series of compound names remain which denote two chief groups of tumours, one of which comprises mixed neoplasms and the other of which bears a mere superficial resemblance to mixed neoplasms.

1. These TUMOURS BEARING A MERE STRUCTURAL RESEMBLANCE TO MIXED NEOPLASMS must be excluded from that category. They comprise those resulting

(*a*) from a secondary (" metaplastic ") change in the stroma of a simple tumour, e.g. " osteocarcinoma " or " osteoplastic carcinoma ", better called " carcinoma with secondary osteoplasia " (resulting from a non-neoplastic deposition of bone in the stroma of a carcinoma);

(*b*) from excessive development of the stroma of a simple tumour as the result of the desmoplastic action of the neoplastic cells on their supporting elements; e.g. " adenofibroma " (= *adenoma fibrosum*), fibrocarcinoma (= *carcinoma scirrhosum*). It may, admittedly, be difficult to draw a sharp line between these cases and those in which the stromal moiety reaches a degree of proliferation and disorderliness indicative of autonomous growth, i.e. an independent impulse to proliferation. This difficulty need not surprise us; it is merely a somewhat more complicated variant of the familiar dilemma which confronts us when we attempt to demarcate the border between hyperplasia and neoplasia: just as we have to decide in the case of proliferations of a single cell type whether we are dealing with hyperplasia or neoplasia, so we have here to assess whether we are dealing with a simple neoplasm whose stroma is hyperplastic or with a mixed neoplasm (whose stromal moiety has actually become neoplastic). Into the class of tumours that we are considering I have already indicated my inclination to place the leiomyomatous carcinomas of birds. In this case one has to deal with a stromal moiety of unusual nature, viz. smooth-muscle tissue, which has been stimulated by the presence of the neoplastic epithelial elements to excessive (apparently almost to the point of autonomous) proliferation. This difficult problem is fully discussed in dealing with the tumours in question (Chapter III), and I am open to correction in my decision to exclude them from the category of mixed neoplasms. Here the difficulty of distinguishing between hyperplasia and neoplasia is encountered in a very acute form, and it is noteworthy that in avian pathology we meet examples in the literature where observers were unable to decide with certainty whether they had to deal with local hypertrophies of smooth muscle tissue or with benign neoplasia (i.e. leiomyoma), where only a single cytological type came under consideration. When (if ever) we should arrive at a satisfactory criterion whereby hyperplasia of smooth muscle may be sharply distinguised from leiomyoma in avians, it would be time to carry this discussion further.

II. MIXED NEOPLASMS (in the strict sense and as defined above) are, on an analysis of their pathogenesis, seen to fall into two chief classes, those that may be conceived as arising from a stimulus to neoplasia affecting a single cell (or group of similar cells) and those whose origin is due to the acquiring of neoplastic propensities by two distinct cell types. These two kinds of mixed tumours may, for convenience, be designated false and true respectively. It must be emphasized that these terms are used essentially from the standpoint of the pathogenesis and are not histological descriptions.

A. *False Mixed Neoplasms.*

(1) It is not usual to include under the category of mixed neoplasms those tumours the duality or multiplicity of whose component cells results from a tendency of the "type cell" to undergo a heteroplastic(¹) differentiation reflecting the normal developmental potentialities which are retained even by the cells of the adult organism. Such a process is responsible for the cytological features of diseases like (i) erythroleucosis of fowls, in which neoplastic lymphocyte-like precursors undergo differentiation into haemoglobiniferous elements which also at first retain the power of proliferation,

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(¹) The term heteroplastic differentiation is employed here in the sense in which it is used by Danchakoff (1918) to denote those grades of unfolding of cellular potentialities which result in the appearance of cells morphologically dissimilar from their immediate precursors; as opposed to the homoplastic differentiation whereby arise cells of the same morphological type as their precursors, from which they exhibit only minor structural divergences. As example of the first type may be mentioned the transformation of the macrophage into the fibroblast or of the myeloblast into the myelocyte; the second type is represented by the differentiation of the myelocyte into the granulocyte or of the erythroblast into the normoblast. The terms are no more than conveniently descriptive and a rigid distinction is not to be looked for.

as they do under the conditions of non-neoplastic haemopoiesis; (ii) the so-called lympho-endothelioma (Hodgkin's disease) where elements of the type of the (fixed) reticulum cell differentiate into (free) lymphocytic cells (as occurs also in non-neoplastic lymphoid tissue); and (iii) the "mixed-celled" sarcoma (of birds) where neoplastic macrophages and fixed reticulum cells differentiate into neoplastic fibroblasts. The result is a tumour tissue composed of two or more cell types (together with the transitions between them). Whether (iv) the thymomas ("lympho-epitheliomas") fall under this group or not we cannot decide until we know how the round cell elements of these tumours arise, viz. by differentiation of the entodermal (epithelial) elements, or by "Inwanderung" as some contend is the case in the normal thymus.

I have mentioned this class of tumours here because, as will be seen, they are so closely related to the first type of neoplasm universally regarded as a mixed tumour and which we shall next discuss.

(2) The tumours (or tumour-like processes) just discussed (1) were seen to be characterised by an unfolding by a single neoplastic cell type of the potentialities which are also possessed by the normal or at least by the non-neoplastic prototypes of these cells in adult life. We have now to consider a group of mixed tumours in which the "type cell" is one possessed of dual or multiple potentialities, but is one which has ceased to exist as such in post-foetal life, for the reason that those potentialities have already fully been realised during embryonic development. Fundamentally, the close relationship of such tumours to those in group (1) is apparent: the admixture of cell types is in both cases due to unfolding of normal potentialities and in both cases (theoretically at least) there would be present transitions between the component cell types. The only difference, from the pathogenetic standpoint, is the persistence of the multipotent prototype cell in the adult in the one case and its exhaustion during embryonic development in the other.

We have here as a typical example the embryonal nephroma, a tumour the plurality of whose cell types is due to the embryonal pluripotentiality of the cells from which it takes origin: the nephrogenic mesoderm being capable of differentiation into both epithelial and connective-tissue elements. And it seems probable to me that the great majority of "embryonal" tumours, including the familiar mixed tumours of the mammary gland, belong here: their origin is to be attributed not to a simultaneous "cancerization" of two separate kinds of cell, but merely to the result of the acquiring of neoplastic propensities by a multipotent (embryonal) cell.

B. *True Mixed Neoplasms.*

A true mixed tumour is to be conceived as the result of the (*a*) simultaneous or (*b*) successive acquirement of neoplastic propensities by two (or more) separate and distinct cell types, which are from the outset situated contiguously. It follows that in such tumours (unlike in the false mixed neoplasms) one does not expect to encounter transitions between the component cell types; in practice (it appears to me) this circumstance is important evidence that one is dealing with a true mixed tumour, and it is on the presence of transitions from the "connective-tissue" cell types to the "epithelial" cell types that I have based my opinion of the nature of the canine mammary tumours, viz. that they are false mixed tumours. It is probable that what I describe as true mixed neoplasms are considerably rarer than is generally believed and that many other tumours considered (if indeed those who discuss them enter into such analysis at all) as arising on the basis of "dual cancerization"([2]) really belong to the false mixed tumours. The successive (b) "cancerization"([2]) of the two cell prototypes in a true mixed neoplasm would be represented in tumours in which, at a time subsequent to the establishment of neoplastic proliferation of the elements of the parenchyma, those of the stroma come to acquire neoplasia: in this way a simple tumour might become a true mixed tumour, for example a carcinoma might at a later stage become a fibrocarcinoma or a sarcocarcinoma, an adenoma a fibroadenoma, etc. As has been pointed out an attempt should be made to distinguish a mere excessive hyperplastic stromal response—(*carcinoma scirrhosum*, *adenoma fibrosum*, *carcinoma leiomyomatosum*)—from actual neoplasia of the stromal moiety. The difficulty of this distinction has been discussed previously.

It will be noted that, in the definition of the true mixed tumour, emphasis has been laid on the original contiguity of the two normal cells which may be conceived as responding to the stimulus (whether simultaneous or successive) to neoplasia. This has been done in order to distinguish the so-called "collision" tumours arising as multiple (e.g. two) independent neoplasms which subsequently unite or intermingle as they enlarge, and which properly speaking do not fall under the category of mixed neoplasms at all. Yet such tumours are obviously pathogenetically quite closely related to the true mixed tumours arising from simultaneous "cancerization" and to that extent are perhaps even more deserving of consideration here than are the false mixed tumours, which owe their origin to a radically different set of circumstances. A good example of this collision process has been described in the fowl (15100—Chapter VII) resulting from a (secondary) intermingling of myelocytoma (myeloid leucosis) with ("mixed-celled") sarcoma. Further examples of this process in animals are afforded by the admixed acanthomas and pigmented epitheliomas in the goat, according to the conception of the pathogenesis of these lesions which has been enunciated by Thomas (1929). He is inclined to regard the acanthoma as arising from the epidermal cells and the pigmented epithelioma ("basal-cell" carcinoma) from the immediately underlying sebaceous gland cells; union of the two neoplastic tissues may occur subsequently as the result of progressive spread from two centres in close proximity to each other. Such collision tumours are closely related to multiple primary neoplasms, for example cases of acanthoma and pigmented epithelioma situated at such distances from each other that secondary

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([2]) There is unfortunately no convenient term whereby to denote "the process of becoming neoplastic" as applied to the cell. "Cancerization" is used here to mean either a malignant or benign neoplastic transformation, i.e. to replace the cumbersome phrase "acquirement of neoplastic propensities" used previously in this passage.

union is impossible; such are seen where an acanthoma may be situated on the head and a melanotic epithelioma may be located in the perineum of the same subject. How do such multiple primary neoplasms differ from collision tumours; and, on the other hand, on what grounds may we exclude the latter, conforming to the strict letter of our definition, from the true mixed neoplasms? Theoretically, the collision tumour might be distinguished aetiologically from primary multiple neoplasms by the possibility that the former may arise as the result of a single(³) carcinogenic stimulus whose effects are diffused among contiguous cells of two different kinds, while the latter may owe their origin to distinct carcinogenic stimuli operating at different points in the body. On the other hand, the mingling of the moieties of the collision tumour might be regarded as quite fortuitous, depending on the chance that two primary neoplasms are as likely to rise at closely proximate sites in the body as at widely separated points. Such a conception of the purely fortuitous origin of the collision tumours would justify our regarding them as special cases of multiple primary neoplasms and removing them altogether from the category of mixed tumours whose dual nature is not the result of chance.

However difficult it may be in practice to apply our classification of mixed neoplasms, I feel that a scheme such as has been outlined above may profitably be kept in mind when considering the problems presented by the individual tumours which are encountered. Lesions which arise on the basis of fundamentally different pathogenetic (and possibly aetiological) processes should be discriminated wherever possible. With the growth of our knowledge the general category of " mixed tumours " may perhaps cease to be the dumping ground for a miscellany of pathological processes having little in common beyond a superficial resemblance of their end results.

Embryonal Nephroma.

The embryonal nephromas of domesticated animals (tumours considered to correspond to the Wilm's tumour of children) are perhaps the best known among swine, in which they have been described by Day (1907), Feldman (1928 and 1930), and Kinsley (1930). Embryonal nephroma is considered to be the most common neoplasm of swine and it is remarkable that in this country not a single case has come to our notice and further that even those with extensive abattoir experience(⁴) have not encountered cases in swine in South Africa. As well as in man and the pig, embryonal nephroma has been described in the domestic fowl (in which, as Feldman has pointed out, it is commoner than is other animals) by Mathews (1929*b*) and also by McKenney (1931) and by Feldman (1932); in the bovine by Feldman, in the rabbit by Polson (1927) by Scott (1917), and by other workers. The Onderstepoort collection

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(³) " Single " is, of course, not used here in the sense of " single in time " as is done in discussions on the aetiology of neoplasms with reference to the rôle of traumatic or irritative influences.

(⁴) e.g. Mr. A. C. Kirkpatrick, M.R.C.V.S., of the Johannesburg Municipal Abattoirs (in a personal communication).

contains ten examples of this neoplasm, five from fowls (Fig. 160), two from bovines, two from horses, and one from the sheep; these two bovine cases make up the total of cases in cattle, recorded under that name to three, while I find no record of the tumour in the horse or in the sheep. But there is little doubt that these tumours have very often been encountered in bovines as well as in other species under other names. At this Institute itself, the cases in bovines had been recorded as adenocarcinoma or adenoma, and that in the ovine as " cystadenoma ", sufficient attention not having been paid to the details of the histology and cytology to disclose the essentially " mixed " nature of the neoplastic tissue.

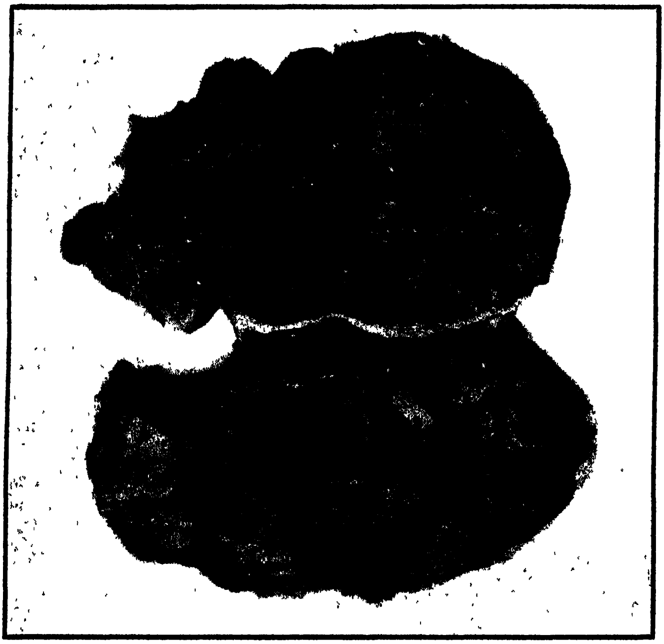

FIG. 160.—Embryonal nephroma of the fowl. (2143 ; 5/6 ×).

It is not intended in this text to describe in detail the histology of these tumours, an excellent account of which in the different species is to be found in Feldman's work. It is of interest to mention the following observations on the Onderstepoort material:—

As is known from the work of Mathews, the disease in fowls usually affects the left kidney or left renal region. In three of our avian cases the left side was affected, in one the right side; while in the remainder there is no record of the side affected. Metastasis was recorded in only one of these cases, but in two cases recorded subsequently to this work metastases were present. They are probably quite frequent, therefore. Feldman states that " mitotic division is usually prominent, particularly in the highly cellular intertubular (i.e. sarcomatous) portions, although this phenomenon is commonly displayed by the lining cells of the duct- or alveolar-like structures "(5). It seemed of interest to ascertain precisely what the growth-rate of the sarcomatous and epithelial moieties was. The results of mitotic counts of these two tissues in fowls showed that there was no constant preponderance of the growth-rate of the solid over the tubular portions: in some cases the counts were approximately equal, although where they were unequal the rate was in favour of the (sarcomatous) intertubular portions. The figures in general appear to confirm the suggestion made by Feldman. In the nephroma from the sheep, no mitoses were seen. On account of the absence of records of this tumour in the sheep and the horse special attention may be drawn to this case (Ovine, 3055). The tumour had the structure of *cystadenoma papilliforme* (as which it had been diagnosed in the routine), but the presence of solid interadenomatous tissue composed of fibroplastic(6) spindle cells with transitions to the epithelial elements, in every way corresponding to the "sarcomatous" portions of the better known nephromas of the pig and fowl, had been overlooked. Similar tumours were encountered in two horses (Figs. 161, 162, 163).

Regarding the diagnosis of embryonal nephroma, the suspicion of this neoplasm should always be borne in mind when tumours of the kidney of the pig, bovine, or ovine, or equine are encountered; or when in the fowl a tumour in or attached to the kidney, or depending from the lumbar region into the peritoneal cavity at a considerable distance from the kidney is encountered. Histologically the diagnosis is confirmed by the finding of spindle cells growing in solid form (and associated with the production of intercellular fibrillar stroma) alternating with epithelial elements (lining acini, or cysts, or papilliform cysts) and (most importantly) of transitions between the two types. In fowls the diagnosis of embryonal nephroma can also be made with confidence when only secondary lesions (e.g. pulmonary metastases) are submitted from the autopsy. In pigs the finding of neoplastic osseous or muscular tissue makes the diagnosis still more obvious, but such moieties are not to be regarded as essentials and are not found in the avian tumours. As Feldman indicates, it may be difficult in the mammalian tumours to demonstrate the "sarcomatous" moiety (Fig. 163): if such demonstration completely fails after examination of representative sections from all parts of the tumour, one has, of course no alternative in the presence of a single epithelial neoplastic moiety but to diagnose carcinoma or adenoma as the case may be. In fowls our experience has been that the "sarcomatous" elements are present in abundance; this may not, however, be the case in the ox, sheep and horse.

We may close this discussion with the remark that although the term "sarcomatous" has been here used to designate the solid, fibroplastic tissue composed of spindle-shaped cells and is also employed in the common designation—adenosarcoma—of these

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(5) Obvious misprints have been corrected in this quotation.

(6) Reticulum fibrils.

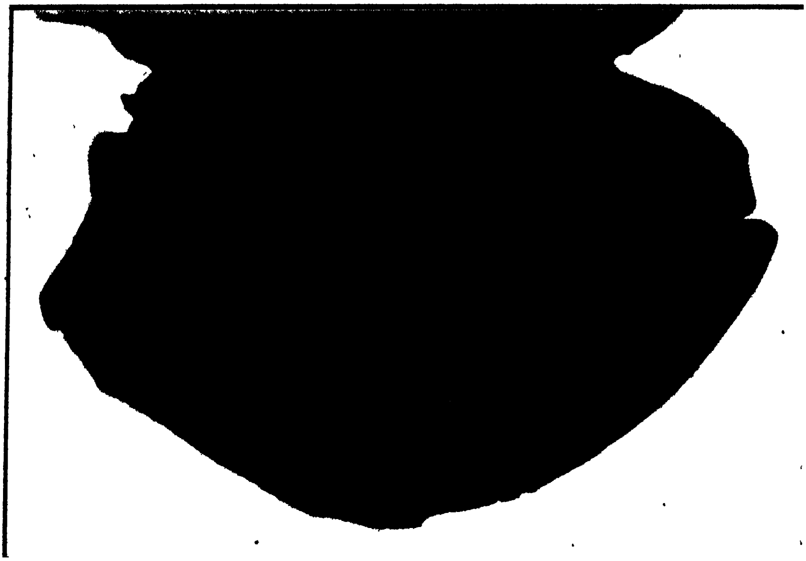

FIG. 161.—Embryonal nephroma of the horse: Remaining kidney tissue at right side of illustration. (3446; 2/5 ×).

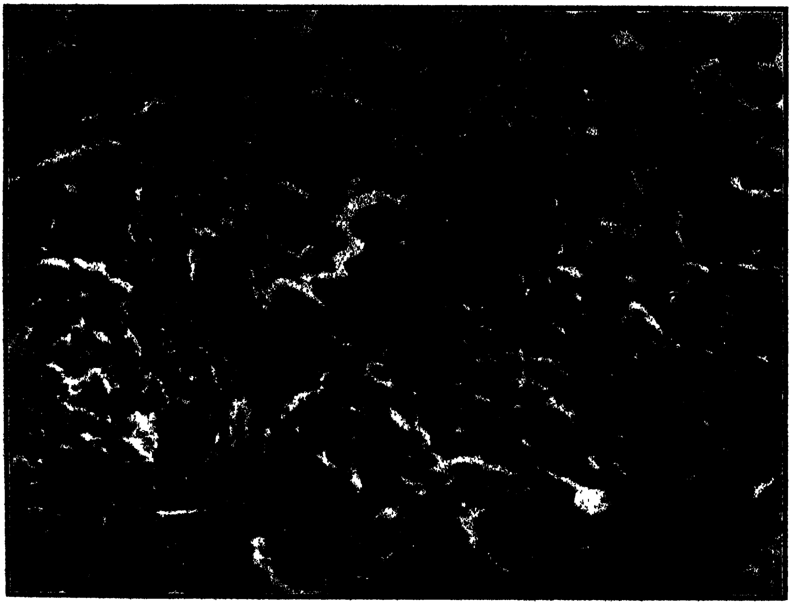

FIG. 162.—Structure of the embryonal nephroma shown in fig. 161: Adjacent areas where adenoid (below) and sarcomatoid (above) growth types predominate respectively—("adenosarcoma"). (3446; 100 ×).

tumours, yet the tissue in question is not comparable to true fibroplastic sarcomatous tissue; frankly collagenous fibres are not produced by these cells as a rule and anaplastic changes are conspicuously absent: the designation embryonal is therefore most suitable to describe these tumours, and one gains the impression that they owe their proliferative power to the embryonic rather than to the malignant neoplastic nature of their cells.(⁷) We shall encounter much the same features among the mixed mammary tumours of the bitch.

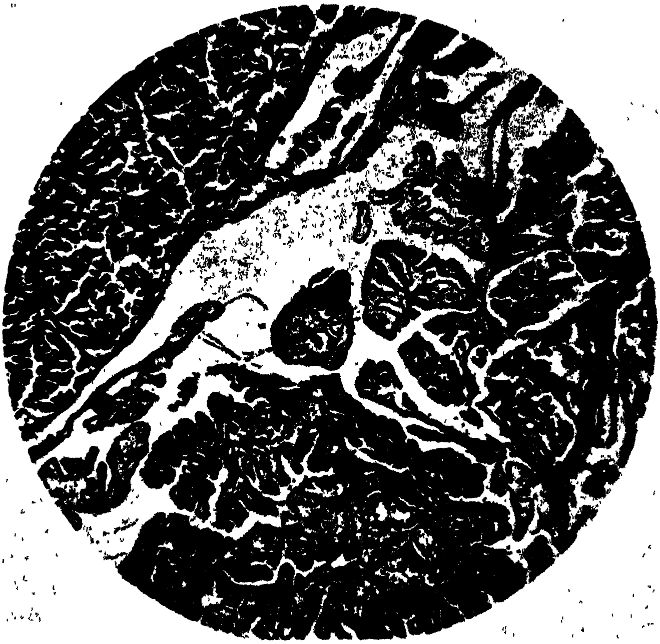

FIG. 163.—Structure of a less easily recognisable embryonal nephroma of the horse: More solid (above) and more cystic (below) papilliform adenomatoid types of growth, with sarcomatoid moiety not readily detectable; haemorrhages into the lumina. (5574; 30 ×).

Mixed Mammary Neoplasms of the Dog.

The great frequency of mixed neoplasms of the mammary gland of the dog is well illustrated by a study of the Onderstepoort collection. Of seven malignant breast tumours in this species, only one presented the structure of a simple tumour (*carcinoma adenoides cysticum et papilliferum*—Canine, 16323). The other six all presented varying grades of the histological structure of mixed neoplasms.

(⁷) I am only too well aware that I am here using inadequate and vague terms to imply a distinction that cannot at present be fully explained. But, as Ewing aptly has it, " the embryonal nature of a tumour should not be confused with an anaplastic character ".

Concerning the propriety of regarding these growths as mixed tumours not a few extreme difficulties exist. With reference to the (common) osteoplasia found in the " stroma " of canine breast tumours, some authors, e.g. Schmidt (1933), incline to the view that this may be ascribed to a secondary change in the stroma of not truly neoplastic character but apparently rather after the manner of Virchow's original conception regarding the origin of bone and cartilage in soft tissue, viz. by " metaplasia " from fibrous tissue. Both T. B. Mallory (1933) and Micseh (1933) support this view of the general origin of bone in carcinoma, but they are not dealing specifically with tumours of the dog's breast. That there occur (simple) carcinomatous tumours in which bone develops in the stroma as a result of " metaplasia " and not as an additional neoplastic moiety no one will deny. We have already mentioned such tumours under the heading of neoplasms having a mere superficial resemblance to mixed tumours, and we have described in a sheep and the dog good examples of " carcinoma with secondary osteoplasia in its stroma " (Chapter II). But the very common occurrence of frankly mixed tumours (" adenosarcomas ") in the breast of the dog, with all transitions to tumours showing varying grades of osteoplasia and chondroplasia, makes one statement safe: although there may be simple tumours of the dog's breast with secondary stromal osteo- or chondroplasia, all cases of hard tissue formation are not explicable on that basis; and the suspicion must remain that if some cases of osteoplasia in canine mammary tumours are to be explained as mixed tumours, all cases may possibly have to fall under this category. After a close study of the mammary tumours of dogs, I find myself unable to make a more categorical statement than the above; but so strongly do I hold the suspicion mentioned that, until proof to the contrary is forthcoming, I class all these tumours under the (false) mixed neoplasms. The demonstration that some cases of osteo- and chondroplasia represent an actual neoplastic moiety besides the epithelial elements throws a strong burden of proof on any who would contend that other cases are to be ascribed to a different pathogenesis; this onus has not yet fully been discharged.

The second difficulty I wish to mention is one which seems to beset the human pathologists more especially. Regarding carcinosarcomas of the human breast, Ewing says that in some such cases he has " not been satisfied that the spindle cell areas were not modified epithelium ", and again with reference to adenosarcomas he opines that " it seems highly probable that some such cases . . . are rapidly growing carcinomas in which the anaplastic tumour cells assume a spindle or rounded form "; on the other hand, Ewing accepts " that most pure sarcomas (of the breast) are identical in origin with adenosarcoma. This view must be accepted at least for the true spindle-cell sarcoma. Not only is their structure identical with that of adenosarcoma, but recurrence of adenosarcoma may take the form of spindle-cell sarcoma ". It thus becomes apparent that, difficult as may be the accurate assessment of the mixed nature of the canine mammary neoplasms, the problems are to be encountered in a still more obscure and confusing form in the mammary neoplasms of man. The moral of this is obviously that the canine tumours, presenting similar problems in more easily soluble form, may well offer material to the study of which more human pathologists (whose experience of mammary tumours is inevitably based on a far larger amount of material than veterinarians can hope to encounter) might profitably direct their attention. Regarding Ewing's confession of inability to distinguish between " sarcomatous " connective-tissue elements and " modified (i.e. spindle-shaped) epithelium ", he does not enlarge on this dilemma as much as one could wish. Nor does he indicate whether by such " modified " epithelial cells he conceives derivatives of (previously) adult epithelium or merely embryonic epithelium assuming a multiplicity of shapes. The " epithelium " of the embryo is a very elastic term, embracing all three germ layers (i.e. every cell of the tridermal embryo) at a certain stage of existence, including the mesoderm (and consequently being ancestral to the derivatives of the middle germ layer). But apparently Ewing means modified neoplastic cells derived from pre-existent adult epithelium; otherwise, as we have seen, his statement lacks meaning on close analysis. Now it would seem simple to propose and carry out as a differential test between true epithelial elements and connective-tissue elements the criterion of the association with intercellular fibrils. If the spindle-shaped cells are epithelial, the modification causing the obscurity of their nature might well be expected to extend no further than so far as their shape is concerned. I cannot believe what Ewing at times seems to be hinting at, viz. that from adult epithelium may be derived cells indistinguishable from fibroblasts; whatever their shape may be, as students of cell potentialities we cannot admit the possibility of the simulation being extended to the production of collagen or reticulum fibres.

It is this very test which, applied to the tumours of the dog, allows one, even in the most difficult of cases to decide that two cell types are concerned, the one related to the connective-tissue cell (in virtue of shape and fibril production), the other clearly epithelial and lining lumina. The fact that all transitions occur between these two elements allows one confidently to place these tumours of adeno- or carcinosarcomatous structure in the category of false mixed neoplasms, to be conceived as arising from the " cancerization " of a single cell type possessed of embryonic potentialities. Indeed the general morphological unity existing among those mixed neoplasms which have purely adeno- or carcinosarcomatous structure is most marked, whether they arise in the kidney (from cancerization of an element of the nephrogenic mesoderm) or in the breast [from cancerization of an (aberrant?) cell with a very similar multipotentiality]. In the absence of the application of the essential fibrillar staining reactions, many of such tumours are doomed to be erroneously diagnosed or misinterpreted, and for this reason the older statistics of " carcinoma " of the breast of the dog are quite worthless from the strictly histological point of view. Few of the older mixed tumours at Onderstepoort, whether of the breast or of the kidney, were correctly diagnosed: in some cases the " sarcomatous " element was overlooked, in others presumably dismissed as representing anaplastic epithelial elements assuming spindle shape. The importance of avoiding such errors is by now, it is hoped, fully apparent from our discussion of the classificatory problems. An example of the actual practical importance to the histopathologist is afforded by the case of a bitch (canine, 14605) from which a primary tumour of the mamma had been ablated and diagnosed as carcinoma, and which came to post-mortem some time afterwards (canine, 15827) with multiple pulmonary metastases and no lymph-borne secondaries! These metastases had the structure of fibroplastic (spindle-celled) sarcoma. Only on a re-examination of the sections of the original breast tumour was it seen that the sarcomatous moiety (present only in some parts of the tumour) had eluded notice, and that the original diagnosis should have been sarcocarcinoma. Although I have said that the lung metastases had the structure of " spindle-celled sarcoma ", even at the time when these secondary lesions were first examined a certain atypicality *qua* " spindle-celled sarcoma " was actually noted in my report although I contented myself with that diagnosis. Re-examining the sections in the light of the information gained subsequently, it now appears to me that this difference from typical " spindle-celled " sarcoma is a genuine one. It is hard to speak on the basis of examination of so limited a number of cases, but I am inclined to be confident that with careful attention to the cytological detail there is no reason why one should not with certainty be able to distinguish the metastases of the sarcomatous moiety of a mixed embryonal tumour of the breast from metastases of ordinary " adult " " spindle-celled " sarcoma. This may be done on the basis of a slight tendency of the cells to assume a more polygonal form, lying closer together (differentiation from " mixed-celled " sarcoma on this basis alone a very subtle one indeed!); and a heavier nuclear membrane (more characteristic of an epithelial nucleus) than is usually to be encountered among neoplastic fibroblasts is seen in many of the cells (here again an inherent difference in the nuclear membrane is only on the basis of considerable experience to be distinguished from a not dissimilar " heavy " appearance resulting from submembranal hyperchromatosis, which is a prominent feature of the anaplastic changes in such tumours); and lastly a slight tendency to encapsulation of the metastases as they reach a larger size. It is not wished to stress too much these nice distinctions, which indeed almost baffle description; but merely to express the opinion that the differentiation is possible and hence that on the examination of the first-received specimen of the above case the diagnosis " metastatic fibroplastic sarcoma " was wrong and should have read " pulmonary metastases of a mixed tumour; primary very probably(⁸) situated in the breast ".

Six cases of mixed embryonal tumours of the mammary gland of the bitch were encountered. The actual histology of these false mixed neoplasms of the dog's mammary gland is reflected by the diagnoses: osteocarcinoma (6060), cystadeno-carcinosarcoma (10345), adenosarcoma (13676), chondroadenosarcoma (15548 and 15758), and chondroadenosarcoma (14695), with subsequent

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(⁸) The fact that one is dealing with a bitch allows one to predict this probability, since the overwhelming majority of mixed tumours in dogs (which do not suffer from embryonal nephroma) are situated in the mammary gland.

pulmonary metastases (15827) growing as a type of (embryonal) "spindle-celled" sarcoma. The descriptions will not be given in detail here, the histology of the canine mammary tumours having already been fully studied by Cornil (1908).

An Unusual Mixed Tumour (Embryonal Epulis) in a Dog.

One of the most interesting and instructive of the mixed tumours in the collection is the following:—

(*Canine*, 7808.)

The subject was an Alsatian bitch which was destroyed on account of a tumour of the lower jaw. There is no detailed record of an autopsy, which was, however, carried out by a professional colleague, all organs showing pathological changes being preserved *in toto*. The specimens consist of the head (Fig. 164), heart, and lungs (Fig. 165). In the region of the body of the mandible there

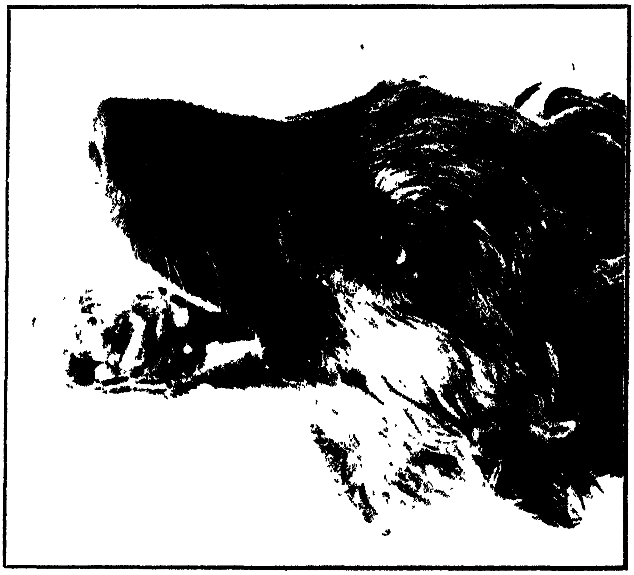

FIG. 164.—A malignant mixed neoplasm ("embryonal epulis") of the gum of a dog. (7808; 1/3 ×).

is (Fig. 164) a large swelling placed more or less in the middle line, but slightly more to the right side of the median plane. It is covered by the mucosa of the gums, which is for the most part intact, but which anteriorly shows superficial erosions. The whole enlargement has an ovoid shape, is elongated antero-posteriorly, and measures 6·5 × 4 × 3·5 cm. It involves the roots of the incisor teeth which appear as if loosely embedded in the tumour, are displaced forwards some 3 cm., and are widely separated from one another. (The left corner incisor is placed 2 cm. from the canine and the others are as much as 1·5 cm. apart.) Both upper and lower incisors are worn down to short stumps and the former close on the middle of the dorsal surface (length) of the tumour, small cavities in the surface accommodating them, while a larger conical depression accommodates the left upper canine in the tumour during closure of the jaws. The tongue rests somewhat displaced to the right side at its apex. The tumour is firmly adherent to the bone. It extends backwards to the second cheek tooth, displacing the first cheek tooth upwards. On section the tumour appears delimited from the covering buccal mucosa. A fibrous " stroma " is seen to enclose rounded areas of a greyish-white (preserved!) " parenchyma " measuring up to 2 mm. in diameter and in which can be seen small, rounded cyst-like cavities, some of which are of pin-point size and visible only under the hand-lens while others reach a diameter of nearly 2 mm. They contain a clear (coagulated) fluid. The knife also encounters spicules of calcified material. The mandibular and pharyngeal lymph-glands appear normal. The lungs (Fig. 165) are studded with numerous, small, scattered nodules varying from 1 mm. to 4 mm. in diameter. Those situated subpleurally cause elevations above the surrounding surface but do not penetrate the serosa. Against the pulmonary tissue these nodules show no encapsulation and have ill-defined borders. They have a greyish-white colour in the preserved specimen. The heart has a " heart-base " tumour attached to it which is described in Chapter XI, being considered unrelated to the gum tumour.

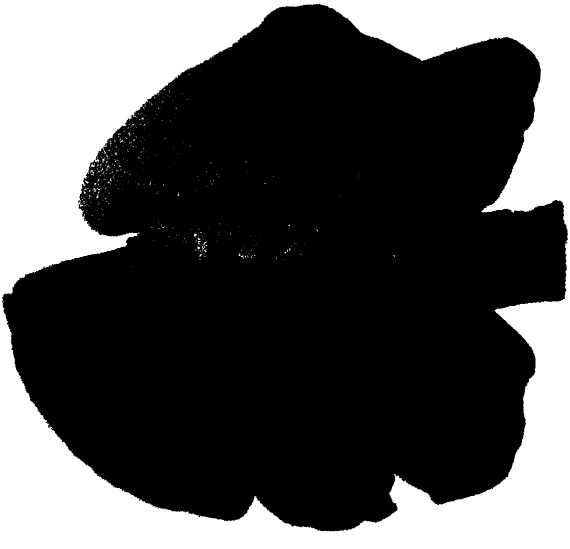

Fig. 165.—Multiple pulmonary metastases of the tumour shown in fig. 164. (7808 ; ×).

Microscopically (Figs. 166, 167, 168), the gum tumour is seen to be strongly encapsulated against the propria of the gingival mucosa. The overlying epithelium is unchanged, except in places where it shows desquamation and leucocytic infiltration (inflammatory changes, doubtless following traumatic injuries inflicted by the teeth and food, etc.). With low magnification (Fig. 166) is seen a rich, very irregular, branching " stroma " consisting of broad bands of collagenous tissue which in parts may predominate over the enclosed " parenchyma ". This " stroma " is in parts dense and

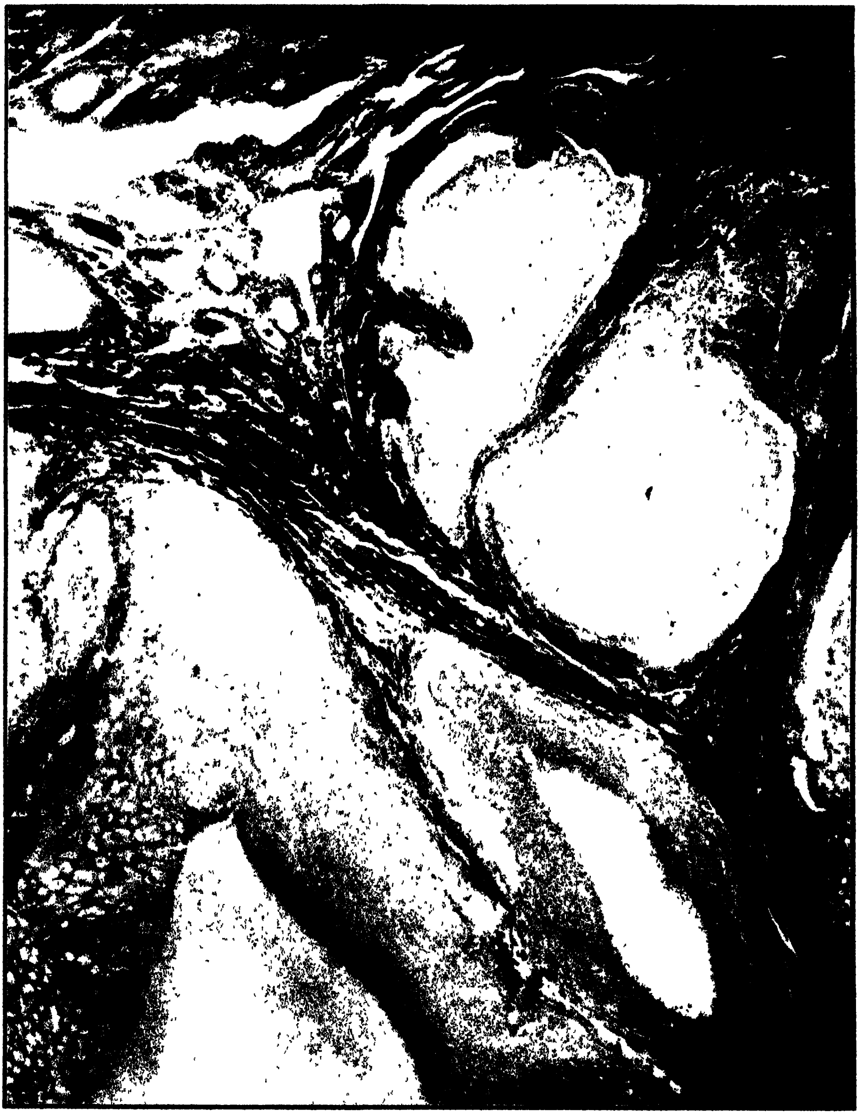

FIG. 166.—Structure of the primary tumour shown in fig. 164: Endotheliomatoid type of growth with formation of small lumina and larger cystic cavities containing lymph; indistinct separation of this tissue from the stroma-like moiety which is also neoplastic and in which osteoplasia occurs. (7808; 33 ×.) van Gieson stain.

highly fibrous, in other parts it becomes cellular and the collagen bundles less prominent. The " parenchyma " exists as larger and smaller, often very extensive islands, which in section usually appear as if completely isolated by the broad bands of " stroma ", or otherwise they may be connected with their neighbours by narrow isthmuses of the same tissue. This appearance under low power is mentioned because the picture at first suggests carcinoma (alveolar structure), a diagnosis which is not borne out by the information gained on higher magnification. This shows that the demarcation between " stroma " and " parenchyma " is by no means sharp and that those terms (which have been used descriptively) are in reality quite unsuitable to describe anything but the crude histological pattern. On closer examination (Figs. 167, 168) it is seen that (*a*) the " parenchymal " cells in many places become continuous with the more cellular parts of the " stroma " and (*b*) both " stroma " and " parenchyma " are associated with osteoplasia.

The cellular " parenchymal " tissue exhibits a considerable variety of cell forms and architectural pattern. In general its elements are closely-packed, oval to spindle-shaped cells most of which have plump, short-oval nuclei but in many of which the nuclei are elongated and often narrow and compressed. These nuclei are poor in chromatin, which is dispersed as a uniform, fine, just visible network; hyperchromasia is not seen. The nucleoli number one or two and are so inconspicuous that the n : N ratio is difficult to measure (e.g. 1 : 200). These cells are arranged in the following different patterns:—

(i) Solid alveoli of oval to spindle-shaped elements arranged without definite order; or there may be a tendency for the cells to be arranged with their long axes parallel, forming ill-defined strands; or in parts there is a limited tendency to arrangement of the cells in solid whorls. Between these elements delicate reticulum fibrils can be seen on appropriate staining.

(ii) The cells may be arranged in many layers to form the thick wall of a cyst-like cavity (Fig. 166, below). The innermost of these cells are usually distinctly flattened from the pressure of the enclosed contents, consisting of coagulated fluid with a fibrinous network (lymph) and a variable admixture of desquamated (degenerated) neoplastic elements.

(iii) The cells may be arranged as flattened elements lining numerous, closely-set, small lumina varying from about 30μ to about 75μ in diameter (Fig. 166, above, and Fig. 167). These cavities contain a few loosely arranged stellate or flattened elements of the same nature as the lining cells, with which they are connected by delicate fibril-like protoplasmic processes. Well preserved blood-cells (apparently in circulation) are also to be seen in these lumina and often the internally-lying tumour cells are related to these in the form of an endothelial membrane whose elements have an unmistakable endothelial habitus and morphology.

(iv) All transitions between the above three types of growth are seen, e.g. alveoli which are mainly solid and only in places contain a few small lumina, or the formation of small lumina in the otherwise solid walls of the larger cavities (Fig. 166 below, left).

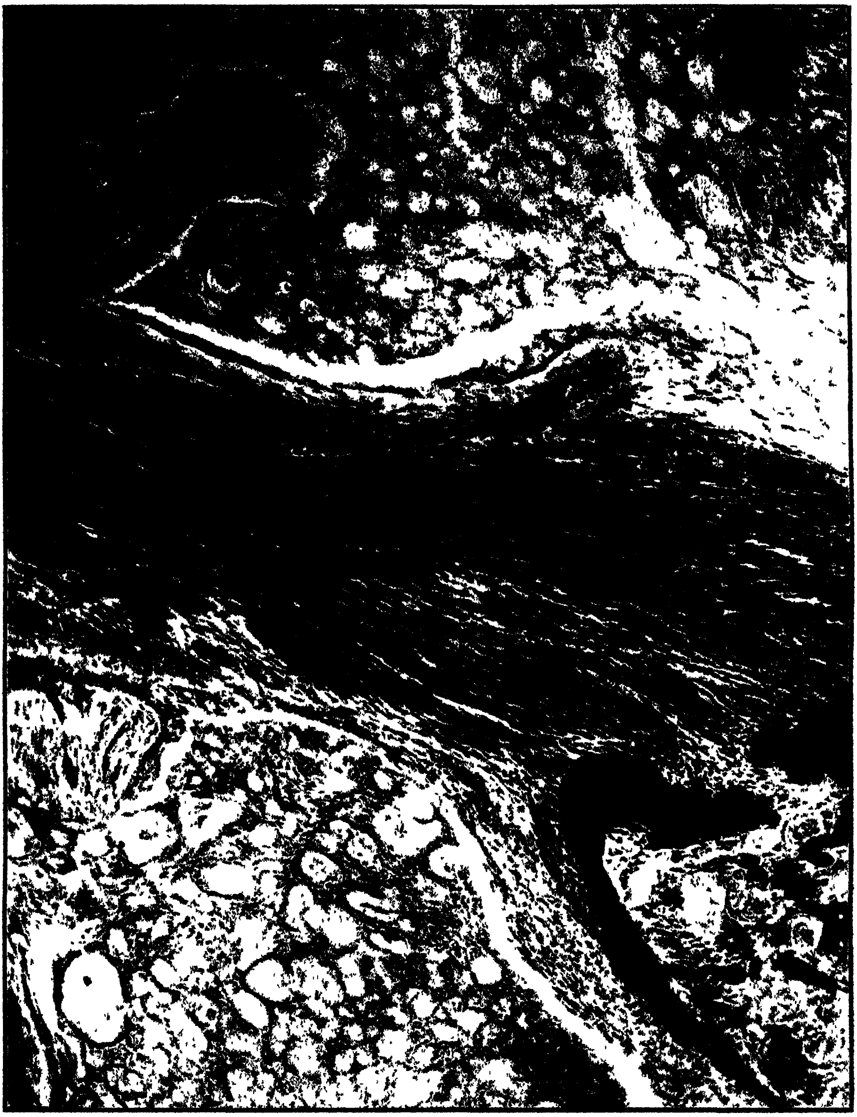

FIG. 167.—Higher magnification of the tumour tissue shown in fig. 166: Sarcomatoid stroma-like moiety and endotheliomatoid parenchyma-like moiety; right, below, transition from "stroma" to "parenchyma" with osteoplasia and "pearls". (7808; 120 ×.) van Gieson stain.

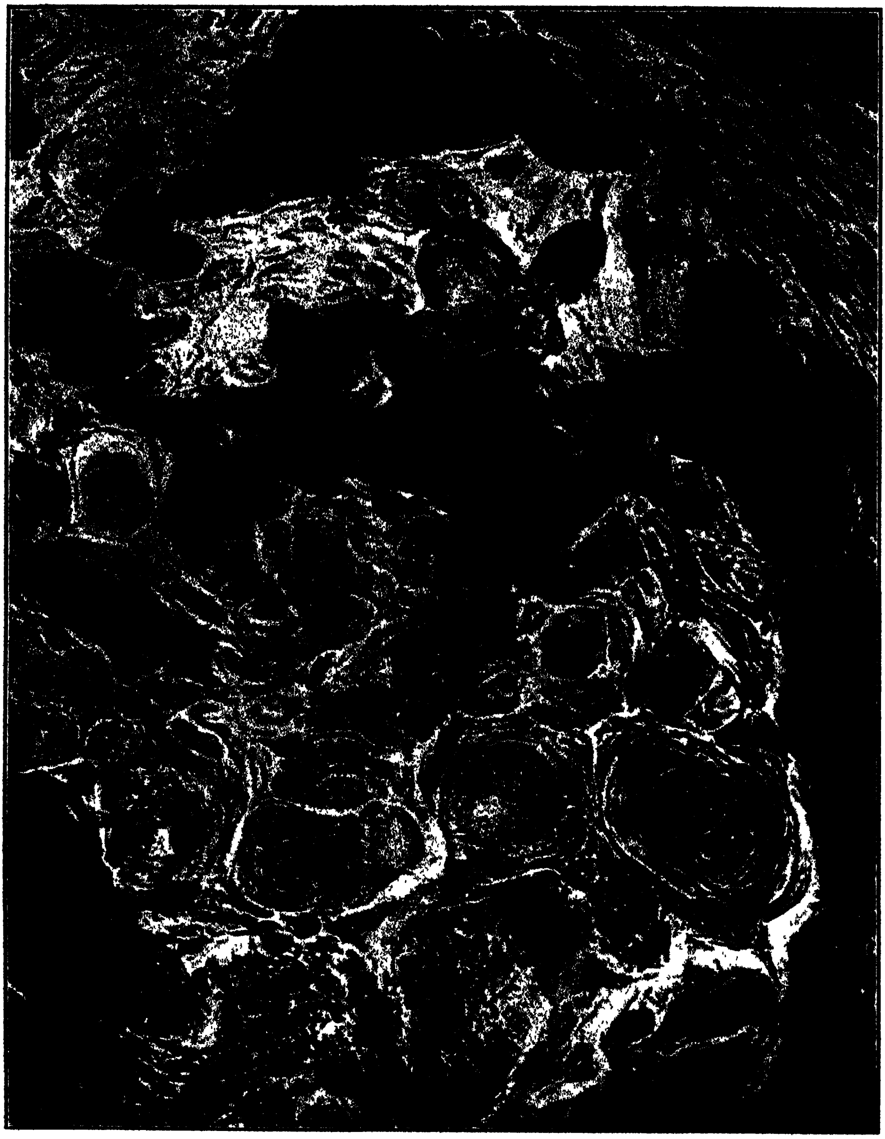

FIG. 168.—High magnification of the field included in the lower right corner of fig. 167: Concentric bodies consisting of lamallae of both keratin and collagen; these anomalous cells are also related after the manner of osteoblasts to the osetoid which is being deposited. (7808; 370 ×.) van Gieson stain.

The further features of this tumour are most conveniently discussed in a consideration of the various intercellular matrices which make their appearance. It must here be reiterated that at the edges of the solid alveoli (i) which are bordered by more cellular parts of the " stroma " the transition from the " parenchymal " elements to the fibroblastic cells forming the trabeculae is a gradual one; it is often impossible, when studying this transitional region to say of a given cell whether it belongs to the peripheral cells of the solid alveolus or to the internal layer of the " stroma ". And the attempt to decide this question is also a fruitless one, because one is convinced that the " stroma " is, in these parts at least, an essential part of the tumour, that it is itself neoplastic, and that the separation of " stroma " and " parenchyma " is a falsity. Further reasons for this attitude will become apparent as the description proceeds.

All stages in the production of osseous tissue (Fig. 166, right, above; Figs. 167, 168) are to be encountered in both the parenchyma-like alveoli and the stroma-like trabeculae (thus demonstrating the similar potentialities of these two moieties), from the deposition of collagen, through osteoid tissue, and culminating in actual calcification. The deposition of pre-collagenous or reticulum fibrils between the spindle-shaped elements of the solid alveoli has already been mentioned. Further, the occurrence of well formed collagenous bundles between these elements in places renders it impossible to distinguish collagenised " parenchyma " from the stroma-like entity. In many parts this deposition of collagen occurs in the form of hyaline, branching strands or masses, against the edges of which cells continuous with the other elements of the alveoli become arranged or condensed in the form of a row of vertically disposed osteoblast-like elements, which become enclosed within the matrix as the deposition of osteoid progresses. These osteoblastic cells do not differ in general morphology from the surrounding fibroblast-like or endothelial-like elements: a somewhat deeper staining reaction of the cytoplasm is, however, noticeable (as is usual in the case of bone-forming cells) and the nucleoli are more prominent (e.g. n : N 1 : 36). These changes progress to the deposition of calcium centrally in the osteoid, whereby variable-sized but small branching trabeculae or more solid plates of bone are laid down whose lacunae are not arranged in Haversian systems. Identical changes can be followed in the stroma-like strands, adding to the impossibility of separating this entity from the " parenchyma ".

A further and most interesting metamorphosis is that cells of the " parenchyma " may occasionally become concentrically arranged and their cytoplasm transformed to form small keratinized " pearls " usually occurring in groups. These " pearls " (Figs. 167, below, right; 168) consist of several concentric lamellae composed of the keratinized cytoplasm (with van Gieson, a pale almost golden-yellow colouration) of whorled cells surrounding one or more central, large, swollen, squamous-like elements constituting the bulk of the body in question and measuring up to 50μ in diameter. In these cells distinct epithelial fibrils and between them intercellular bridges can be seen (prickle-cells). It must be emphasized that these cells having the morphology of squamous epithelial elements and taking part in this pearl formation are intimately related to the osteoblastic elements bordering the osteoid which is being laid down: not only can actual physical continuity be traced between these two cell types by means of cytoplasmic processes, but two forms of intermediate cells occur between the epithelial-like and mesenchymal-derivative-like elements—firstly, cornefying elements standing in relation to the osteoid tissue as osteoblasts and actually becoming enclosed within the matrix as keratinized osteocytes; and secondly, actual admixture of material reacting for collagen within the substance of the cells entering into the formation of the lamellated pearls (Fig. 168), i.e. intracellular collagen formation and keratinization proceeding in one and the same cell(⁹).

Mitotic figures are rare, one being encountered per many hundreds of (high power) fields (M.I. = <1).

The miliary pulmonary nodules prove to be unmistakable metastases from the gum tumour, the essentials of whose microscopic structure they reproduce (Fig. 169). They consist of solid strands of the same endothelial-like elements intermingled with fibril-forming spindle-cells. The same deposition of collagen, osteoid, and bone are seen. Small lumen formation as in the angiomatoid portions of the primary is not prominent, although detectable. This tendency is largely replaced by the following arrangement (Fig. 170). The cells tend to assume polarity and columnar form, being radially arranged to line acini whose lumina are partially filled with desquamated elements. These cells are very definitely epithelial in structure and arrangement and their protoplasm is finely vacuolated as if filled by secretory droplets. They much resemble the elements of a serous salivary gland in this respect, as well as in the appearance of the small tubular lumina which they enclose and in which (in addition to the desquamated cells) the serous secretory product may be seen. At the edges of the foci (which are unencapsulated and are invading the pulmonary tissue) important information regarding the reason for this growth-mode is to be observed (see Fig. 170); here is seen an intra-alveolar spread of the neoplastic cells in the lung tissue. Thus in a pulmonary alveolus bordering the nodule it may be seen that the part of the alveolar wall nearest the tumour tissue is lined or replaced by the serous-epithelial-like tumour cells, which have not yet spread around that part of the circumference of the alveolus which is remote from the tumour. This phenomenon convinces one that it is the pulmonary alveolar walls which, by forming a suitable framework, are responsible for encouraging this acinar growth of the tumour cells. In these secondary tumours the cells show a slight increase of anaplasia as compared with the primary: moderate hyperchromatic changes are to be seen in the nuclei of the endothelioid neoplastic cells as well as minor variations in nuclear shape. Pycnotic nuclei are common. Many minute metastases, invisible to the naked eye, are seen on microscopic

(⁹) It is perhaps advisable to say that the interpretation of these very unusual cytoplasmic transformations has not been undertaken lightly or without earnest consideration of their implications. But the microscopic appearances are quite convincing, although it is of course impossible to indicate the critical staining reactions by photography.

examination of the lung. These are often degenerate and among their necrobiotic cells many small acuminate crystals are deposited, or there may be pronounced neutrophil infiltration.

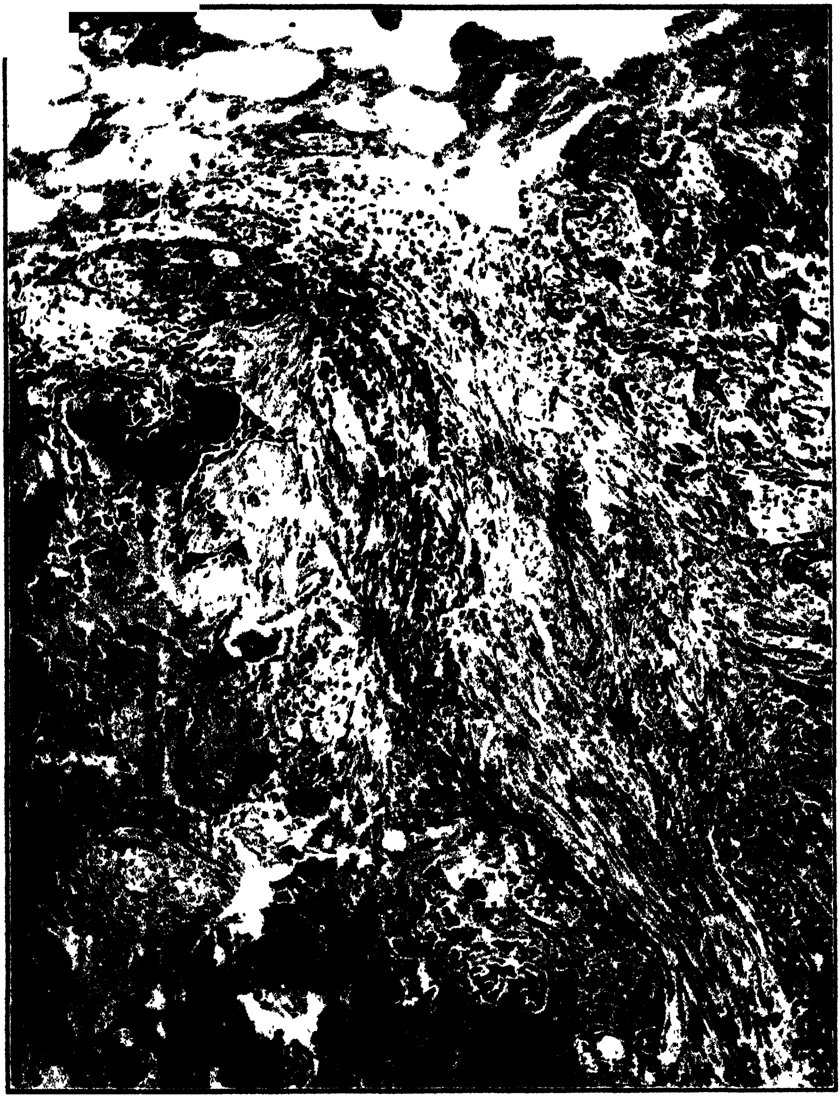

FIG. 169.—Structure of the pulmonary metastases of the tumour shown in figs. 164 to 168: Endotheliomatoid type of growth with areas of osteoplasia; above, the lung tissue. (7808; 120 ×).

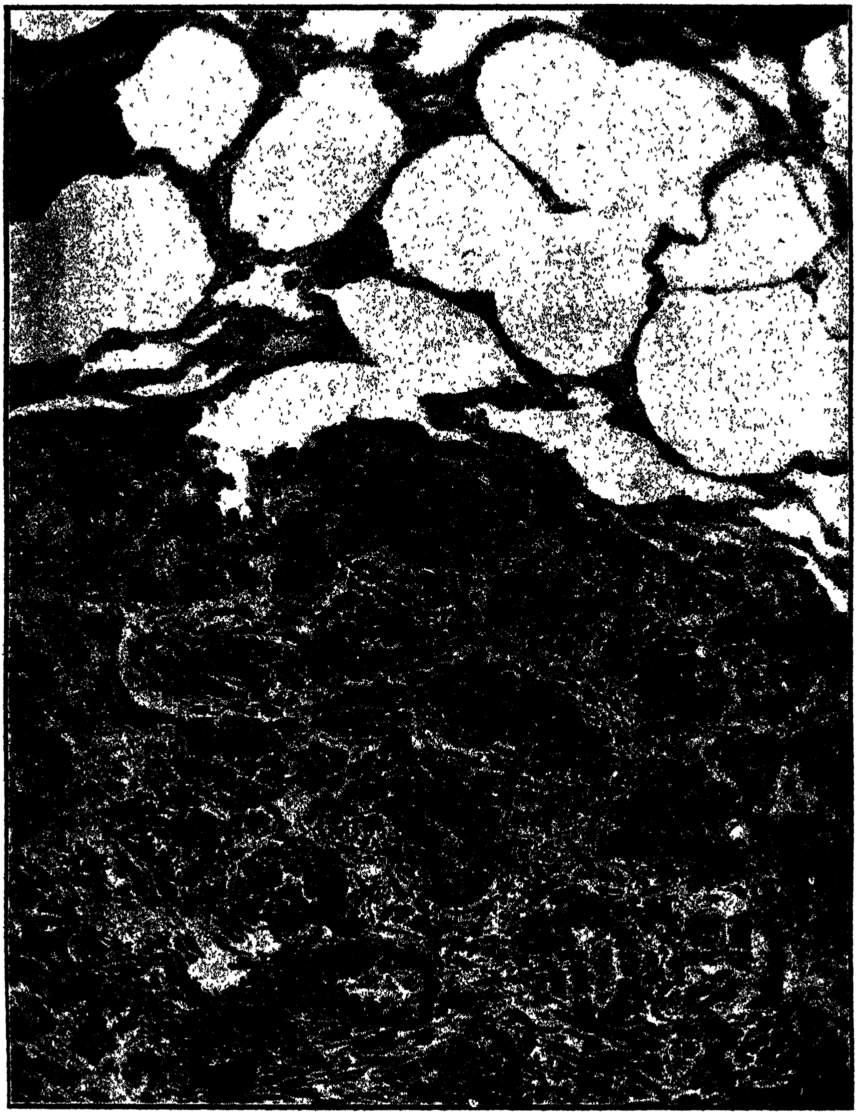

FIG. 170.—Another of the pulmonary metastases shown in fig. 165 : Assumption of an adenomatoid type of growth as the neoplastic cells line-out the pulmonary alveoli; note the partial lining of an alveolus by columnar cells in continuity with the neoplastic tissue just above the centre of the field. (7808; 250 ×).

Discussion.—The primary tumour shows the following histological types of growth: solid and angioplastic endothelioma; fibroplastic (spindle-celled) sarcomatous transformation; osteoma; and pearl-formation with prickle cells somewhat reminiscent of acanthoma; in the metastases there is also a pronounced tendency to grow as adenoid carcinoma. This latter growth-mode, whereby lumina are lined by secretory epithelial-elements, is not to be interpreted as an example of a decrease of anaplasia in secondary tumours as compared with the primary—(a phenomenon which would form an exception to the very general rule that secondaries are at least equally if not more anaplastic than their primary)—but rather by the conception that the potentiality of the tumour cells includes the ability to form glandular epithelium; this tendency not being realised where growth occurs in the hard, relatively unyielding structure of the gums, but being readily unfolded in the lungs, where the alveolar walls form a type of scaffolding which invites the tumour cells to form acini and where the space provided by the alveolar lumina allows room for the assumption of columnar shape. One is struck by the resemblance of this tumour to the mixed salivary gland tumours of man, similar tumours to which may also be found in the gums and elsewhere. The endotheliomatous type of growth encountered in such tumours has been responsible for a well-known theory of their endothelial origin in man, a very understandable deduction from the morphology. In more recent times these tumours have been considered rather of epithelial origin; and Ewing, who discusses this question very fully, is willing to ascribe to such epithelium the property of forming matrices characteristic of connective tissue (fibrils, cartilage, etc.), a conception which is of course repugnant to those who hold to the specificity of the adult germ layer derivatives. His conclusions on this subject are as follows (*Neoplastic Diseases*, p. 775): "(1) The endothelial origin has been disproved. (2) No single source of the mixed tumour meets all requirements. Some are distinctly adenomatous, and probably arise from the acini and ducts of the (salivary) gland in which they are well incorporated. Others are encapsulated or extraglandular, and take the form of basal cell or adenoid cystic epithelioma. These probably arise from misplaced and, occasionally, embryonal portions of gland tissue. Branchial remnants may possibly be connected with this group. (3) The derivation of mucous tissue and cartilage from gland epithelium has been satisfactorily proved, and there is no necessity of including in the originating tissue any cartilaginous structures " One is not, however, inclined to believe in a metaplasia of cells derived from adult epithelium into tissues which are usually the derivatives of the mesenchyme: one sees in the false mixed tumours, wherever they may arise (breast tumours of the dog, embryonal nephromas, salivary gland tumours) a single problem constituted by pathological growth-processes, which on analysis present such closely similar features that one looks for a single histogenetic explanation to cover these diseases. The present case presents similarity especially to the mixed mammary tumours of dogs, in which also may be observed the transformation of cells growing in solid form into spindle-shaped elements associated with connective-tissue fibril production and into osteoblasts associated with bone formation. An endothelial origin for this largely endothelio-matoid and angiomatoid neoplasm is not to be thought of, both on account of the transformation into clearly epithelial cells and of the formation of keratinized pearls—(" pearls " found in endotheliomas have hyaline centres, i.e. are collagenous in origin or may even be calcified, but, e.g. according to Ewing, " prickle cells and kerato-hyalin granules are absent in endothelial tumours ").

This tumour is best explained on an embryonal basis: a false mixed tumour arising from the proliferation of cells, originally identical in type, but unfolding various embryonic potentialities as growth proceeds, especially under the modifying influences of their varying environment at different points. The fact that squamous epithelium, glandular epithelium, endothelium, and connective-tissue derivatives are formed gives rise to the suspicion that the cell or cell-group from which the tumour arose might have been set aside at a time prior to the completion of the differentiation of the germ layers. It seems to me very unimportant to name these mixed tumours histologically, except from the point of view of a convenient summary of the actual histological structure: if such a name is desired for this tumour it would be osteo-fibro-sarco-carcino-endothelioma. On the other hand more information is to be conveyed by bringing such tumours into line with the tendency to name embryonal tumours according to their position in the body (e.g. nephroma). Epulis is a general name for tumours of the gum and by that name the present tumour is conveniently designated.

Diagnosis.—Embryonal epulis (i.e. a mixed tumour of the gum composed of cells of embryonic potentialities) with multiple pulmonary metastases.

Note.—The tumour of the base of the heart in this subject was originally mistaken for a further metastasis of the gum tumour. But it is an independent primary tumour having no relation to those which have been discussed and it is to be described under the heart-base tumours of the dog.

An Interesting Mixed Neoplasm of the Lung of a Sheep.

(*Ovine*, 5382.)

The subject was a sheep which died as the result of bleeding for the preparation of bluetongue vaccine(¹⁰) and in one lung of which a solitary, pea-sized nodule was present, situated in the lung substance but visible through the pleura. It was described, on section, as being of a greyish colour. It appears sharply circumscribed.

Microscopically, the whole focus is well circumscribed, although a capsule is totally lacking. It consists of (1) a central portion, constituting the bulk of the focus, in which the lung parenchyma has been completely substituted by the neoplastic tissue to be described

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(10) Since the numerous sheep which die from such a cause at this Institute are subjected to a scrutiny serving the purposes of meat inspection only, no detailed autopsy record exists in this case.

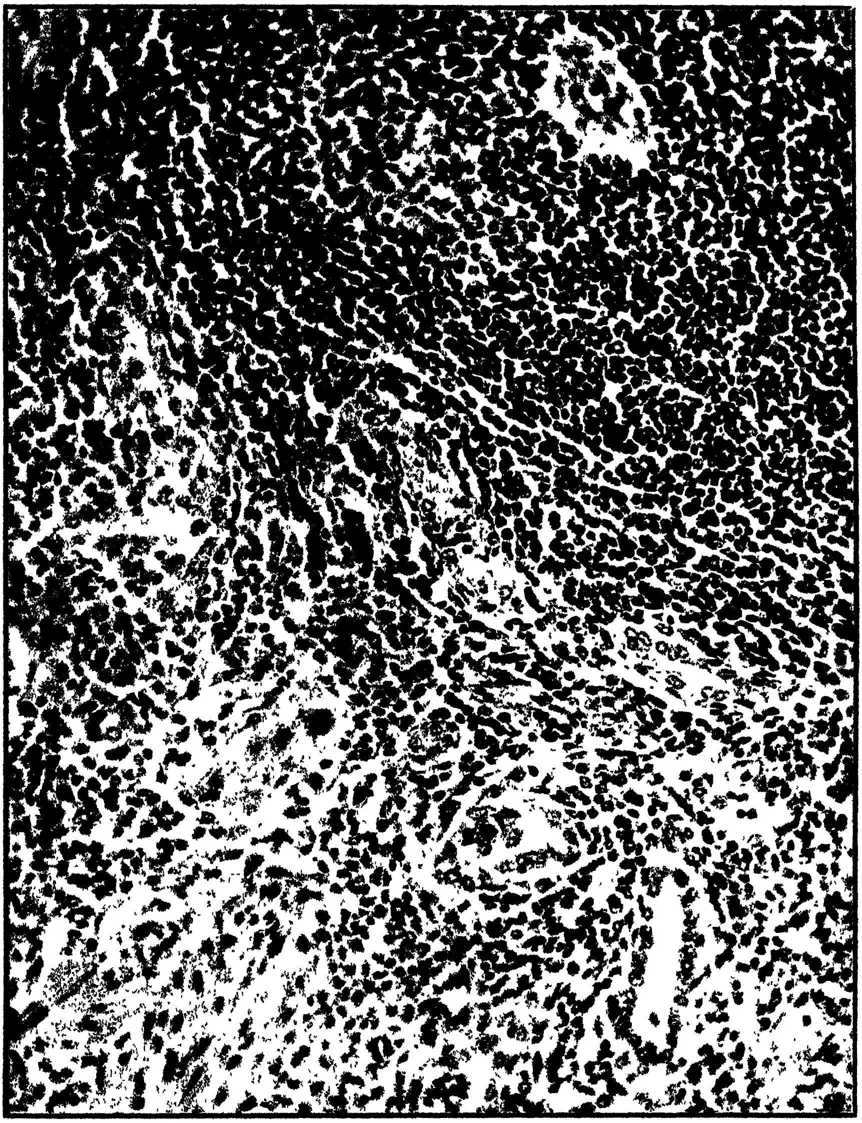

FIG. 171.—A teratoid mixed tumour of the lung of a sheep: Note simulation of the structure of the spleen; above, right, lymphoid type of tissue resembling a Malpighian body with central arteriole and "germ centre"; left, strands of neoplastic smooth muscle representing splenic trabeculae; below, right, adenomatoid epithelial tubules; between these moieties a tissue simulating the red pulp and containing myelocytes. (5382; 250 ×).

and (2) a fairly broad peripheral zone into which the first zone passes without demarcation and which consists of lung tissue still in process of being replaced by the neoplastic tissue. This peripheral zone has a sharp boundary against the normal lung tissue.

(1) The bulk of the nodule is composed of a tissue which at once impresses one by its resemblance to splenic tissue (Fig. 171): The trabeculae are represented by prominent, irregularly arranged and dispersed, variable-sized, branching bundles of atypical smooth-muscle fibres, whose nuclei often show irregularities of outline; the white pulp (Malpighian bodies) is completely simulated by circumscribed aggregations of small and medium lymphocytes supported by an inconspicuous cyto-fibrillar reticulum as in the normal lymphoid nodule. Each is provided with a " central arteriole " (and its branching system of delicate capillaries or precapillary arterioles) which usually lies eccentrically in the nodule. Distinct secondary nodules (germ centres) are not seen, but areas of greater condensation of the elements of the cellular reticulum with rarefaction of the clearly lymphocytic cells occurring near the centres of some of the nodules fully correspond to such structures; the bulk of the tissue in which the lymphoid nodules and the muscular trabeculae (as seen in section) lie dispersed is comparable with the red pulp of the spleen or haemal node tissue. It is composed of cells of the fixed reticulum or reticulo-endothelial type which form a cellular syncytium with associated reticular fibrils and with haemic elements, and which line sinusoidal spaces containing free blood-cells—in other words, corresponding to the sinusoids and intervening cords of Billroth in the normal spleen. The most noticeable departures from the structure of the red pulp of the normal spleen are (firstly) that the haemal elements mentioned are almost exclusively eosinophil granulocytes, fewer lymphocytes and scarcely any erythrocytes being found in the tracts corresponding to Billroth's cords; and (secondly) that as compared with the cellular reticulum of normal spleen, the supporting cells in this tissue are much more prominent—they appear " mobilized ": they are less regular in size and shape, their nuclei are often hyperchromatic, their nucleoli may be somewhat enlarged (e.g. n : N = 1 : 25) and blotchy, mitotic figures may be seen among them (not frequent) and if a careful search be made evidence of the transformation into eosinophile leucocytes (viz. the presence of eosinophile myelocytes) can be detected. In this spleen-pulp-like tissue lie dispersed many gland-like acini lined by a single layer of cells having the morphology of columnar or cuboidal epithelium. The lumina of these tubules contain the desquamated lining elements and often also many eosinophile granulocytes, forming thus an exudate. Such regular lining of the acini by a single layer of epithelial elements with well-preserved polarity does not always obtain; the acinar walls may be thickened to several layers of irregularly disposed cells and there may be obliteration of the lumen by an ingrowth of the epithelial elements whose pedunculated base is continuous with the lining cells. Under such conditions signs of anaplasia may become apparent, the n : N ratio becoming increased from less than 1 : 50 to 1 : 14 or even 1 : 9. In such " papilliform " ingrowths the cytoplasmic boundaries are not distinct and multinuclear masses of cytoplasm are prone to occur; this cytoplasm may

show regressive changes (eosinophilia, etc.) and the nuclei pycnosis. The result is the production of pictures very reminiscent of those seen in certain productive or hyperplastic pneumonias, in which the pulmonary alveolar lining cells are considered to proliferate, filling the alveoli with multinucleated cytoplasmic masses spoken of as giant cells (e.g. in the disease jaagsiekte of equines). Lumen-formation may fail in these epithelial cell-aggregations; and especially in such cases, but also in the case of the lumen-containing alveoli, it was my impression that there are transitions between the reticulum cells of the pulp and the epithelial elements; certainly there are often to be found condensations of cells of intermediate type, and the lining cells of the acini are often apparently in continuity with the reticulum-cells of the surrounding pulp. Further, a pronounced flattening may often be seen in the case of the acinar lining elements, which did not impress one as being the result of mere accommodation to the pressure of the (often scanty) exudate, in fact from the morphological standpoint one may with justification assert that acini occur which are lined in part by typical columnar epithelium and in part by typical (flattened, endothelial elements.

(2) In the peripheral zone of the nodule, the presence of the lung tissue is still recognisable; there are the compressed or almost obliterated pulmonary alveoli whose walls are invaded by the eosinophile leucocytes and strands of atypical plain muscle. The epithelial acini also occur and have to be distinguished from still persisting bronchioles with their more regular lining of ciliated cells. Mitotic figures may sometimes be seen among the neoplastic epithelial cells. These neoplastic acini appeared, as in the case of the pulmonary metastases of the dog tumour (7808) previously described, to be formed by the proliferating epithelial elements using the framework provided by the pulmonary alveolar walls as a stroma along which to grow. As has been said, the transition from the central zone of replacement to the peripheral zone of progressing invasion is a gradual one.

Discussion.—This is a tumour, apparently of embryonal type, in which, besides the imitation of splenic structure, epithelium is formed. In my opinion this growth also, like those we have discussed, falls under the class of false mixed neoplasms (teratoid mixed tumours), i.e. I am willing to believe that all its elements may be ascribed to the proliferation of a single persistent embryonic cell (or cell-group). It may be argued that since epithelium is formed as well as mesodermal derivatives, we should think here of a didermal teratoid tumour; but I feel that those appearances are genuine which lead one to believe that the reticulum-cells, capable of lining blood-sinusoids and transforming into granulocytes, have also the potentiality of growing as epithelial elements—a potentiality which is exercised only under favourable environmental conditions, viz. when a pre-formed " scaffolding " encouraging an alveolar type of growth is already present. Such a stroma is provided by the walls of the hollow pulmonary alveoli and over it the cells (both in this case and in the case of the lung metastases of dog 7808) grow along the path of least resistance, i.e. they line-out the alveoli[11]. [One cannot help thinking, apropos of this discussion, of the doubtful nature (epithelial—i.e. entodermal—or mesodermal) of the pulmonary lining cells themselves, and further of the peculiar intra-alveolar proliferation which characterises the disease of sheep known as jaagsiekte. Has the occurrence of a tumour such as has been described, in the same organ (lung) of this same species possibly a hint to offer us in connection with these two problems? I am not in a position, nor is this the time to enlarge upon what is merely mentioned as a suggestion; nor do I wish at this juncture to express my suspicions in any more concrete a form. But the facts that what may not inaptly be termed neoplastic splenic tissue can grow in the lung of a species of animal to which jaagsiekte is peculiar, that the cells capable of forming such spleen-like tissue may also transform into epithelial elements lining lumina and exhibiting papilliform ingrowths[12], that here also, although there is no encapsulation and the neoplastic tissue has the power to grow invasively in the pulmonary tissue, the whole focus nevertheless remains circumscribed with reference to the surrounding pulmonary parenchyma and does not (apparently) give rise to metastasis[12]—all these appear significant and deserving of the attention of those interested in the pathology of that most puzzling and peculiar disease, ovine jaagsiekte].

This lesion was routinely diagnosed as "leiomyoadenoma"; the observer making the routine report had apparently not been struck by the extraordinary resemblance to spleen, which is not surprising when one remembers that he was examining lung. But if a name must be given to it, the above is quite inadequate. A term fully conveying the histology of this tumour and modelled on the accepted principles of oncological nomenclature is not easy to devise: perhaps "lympho-(reticulo-)endothelio-myelo-leiomyo-adenoma" might serve. But how futile it seems to waste one's time in devising such farcical curiosities of nomenclature! The tumour is a mixed neoplasm characterised by a remarkable reproduction of splenic structure, by "myeloid metaplasia" of that tissue, and by the presence of an adenomatoid moiety.

Diagnosis.—Mixed (embryonal) tumour of the lung.

Other Mixed Tumours in the Collection.

A benign tumour situated in the subcutis of the face of a sheep (Ovine, 8187) was diagnosed as a fibrolipoma. It was considered that the irregularity and pronounced development of bundles of collagenous tissue favoured more this diagnosis than that of *lipoma fibrosum*, but as has been seen, a dividing line between excessively developed stroma in a simple tumour and two independent neoplastic moieties is hard to make, more especially when, benign tumours being concerned, one cannot be guided by signs of cellular anaplasia.

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(11) To place my meaning here beyond doubt, I had best say that I should be prepared to see non-neoplastic embryonic splenic reticulum cells also form epithelium if (e.g. in tissue culture) they could be brought into relation with a sub-stratum whose geometrical form provided a background suitable for an acinar type of growth. If the environmental "stage" be set, the (cell) "actors" will respond by playing appropriate parts.

(12) cf., in each case, the pathology of jaagsiekte.

Leiomyolipoma of the vagina of a bitch (14715) was encountered (Fig. 172) and deserves mention since there is no record in the literature of such a tumour affecting the vagina.

A tridermic teratoma affecting the testicle of a cock (Fowl, 9195) and a didermic teratoma of the ovary of a hen (11866—Fig. 173) were also encountered. A dermoid of the ovary of a cow (6048) has been described by Quinlan (1929). An embryonal hypernephroma has been described among the tumours of the adrenal (Chapter VIII).

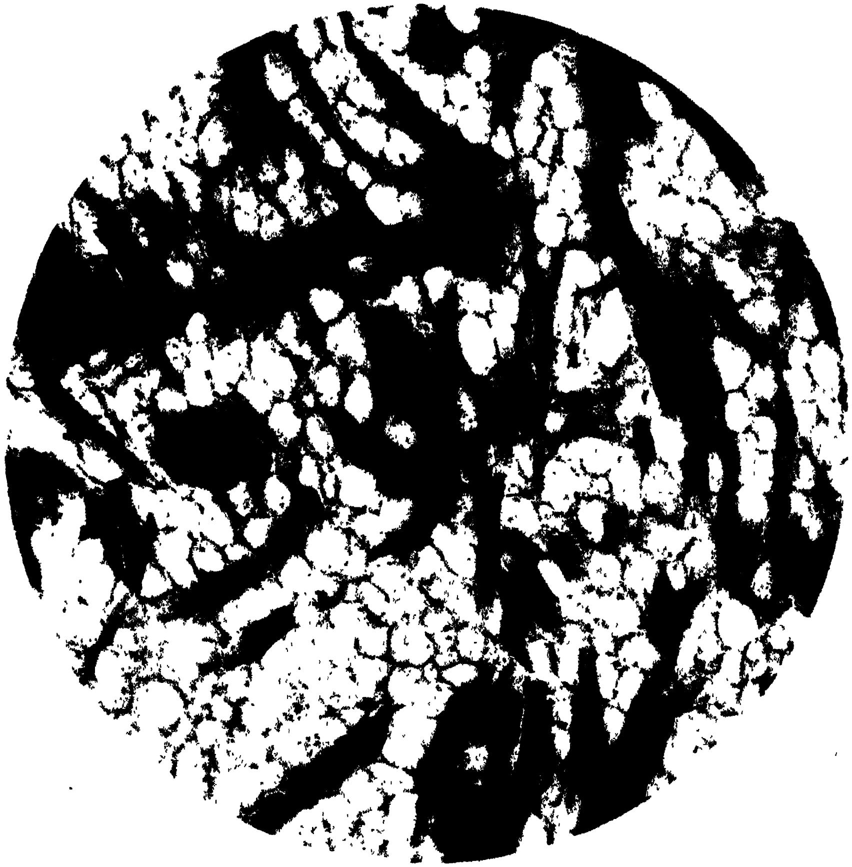

FIG. 172.—Leiomyolipoma of the vagina of a dog: Irregularly disposed strands of smooth muscle in lipomatous tissue. (14715; 75 ×).

A large number of tumours have on consideration not been classified under the mixed neoplasms. These include tumours with a hyperplastic stromal moiety. Such are common in the fowl and comprise especially *carcinoma leiomyomatosum* and *leiomyoma haemangiomatosum*. It has already been mentioned how often the stroma of tumours of the avian female reproductive tract have a smooth-muscular stroma which is extremely hyperplastic. These tumours were not considered to be appropriately termed leiomyo-carcinomata or adenomyomata. Further, in the common leiomyomata of the fowl all grades of vascular development are to be seen. These growths are in the same way not suitably designated haemangio-leiomyomata: we do not consider the vascular element to represent a separate neoplastic moiety.

We have previously mentioned the undesirability of including carcinomas characterised by osteoplasia in their stromas as mixed tumours (osteocarcinoma). Such growths have been discussed under

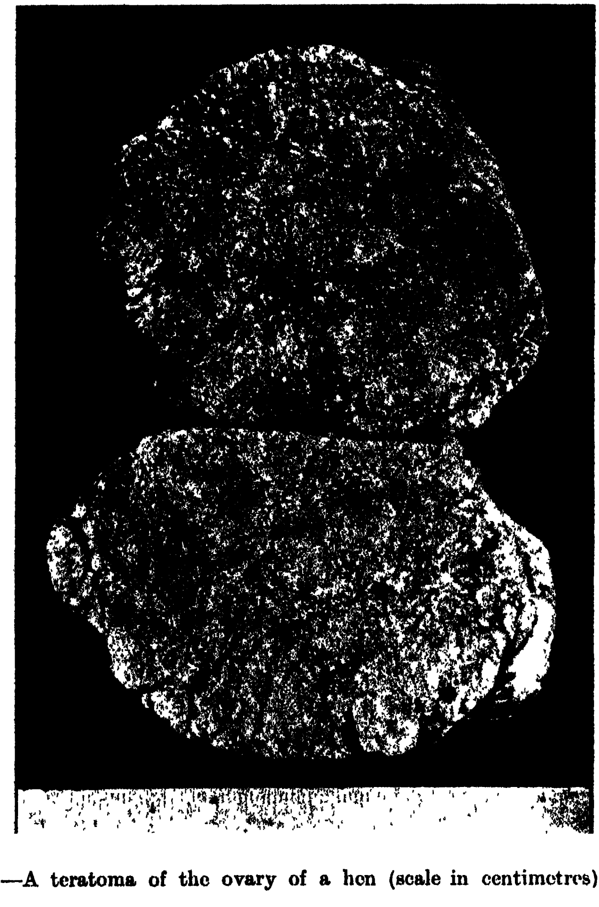

FIG. 173.—A teratoma of the ovary of a hen (scale in centimetres). (11866).

the carcinomata. After some hesitation it has also been decided to classify under the simple tumours one of the fowl (15063) characterised by a fibro-osteo-chondromatous structure, the heterogeneousness of the tissue being considered the result of nothing more than the expression of the normal potentialities of the connective-tissue cell which may be retained even under adult conditions, i.e. it was not necessary to explain such a tumour on an embryonal basis. It has been mentioned among the benign connective-tissue tumours.

Finally, in accordance with the views of Joest, the common equine "cholesteatomata" are not considered here because they represent a non-neoplastic process. I refer to the "newgrowths" commonly affecting the *telae choroideae* in this species and often encountered at this Institute, although but seldom collected as specimens. There are, of course, more truly neoplastic "cholesteatomata" of a different nature, such as those epidermoid cholesteatomas found not only in man but also (rarely) encountered in horses by Bonnet (1880-1), M'Fadyean (1902), and Joest (1921). We have no such cases, however, in our collection, all being of the common plexus cholesteatoma type which are considered by Joest to arise as chronic inflammatory newgrowths (granulomata) caused by the deposition of crystalline cholesterin in the *telae*.

A Note on Fibro-epithelial Tumours of the Skin and Mucous Membranes.

No one who makes a study of neoplastic proliferations of the skin of bovines and equines and of the buccal mucosa of dogs, at least as they occur in South Africa, can fail to be dissatisfied with the existing methods of classification. Since, in human pathology, although the matter has been the subject of considerable controversy, papilloma has come to be treated as a (simple) tumour of epithelium, there has been a tendency in veterinary pathology to follow (perhaps somewhat blindly) in the same direction. But observation of the histology of skin tumours in animals leaves one convinced that, granted that we are dealing with true neoplasms, then true mixed tumours are concerned, i.e. fundamentally, a dual and more or less simultaneous proliferation of both the (epithelial) elements of the epidermis (or mucosa) and the (connective-tissue) elements of the cutis vera (or propria). This duality of the response to the cause of the lesions has been emphasised by Wirsching (1913), dealing with bovine cutaneous papillomatosis.

Papillomata are well known in domesticated animals, viz. in the dog, a species in which buccal papillomatosis is very common (Fig. 174) and in the bovine, in which skin papillomatosis is an equally universal disease (Fig. 175). Both these conditions have been shown to be experimentally transmissible by filter-passing principles, and to affect chiefly young animals(13). They are also exceedingly common, as is well known to any observer of animals: but one cannot expect the incidence of such tumours to be reflected by the statistics of an institute of pathology, both because the diagnosis is usually obvious, even to the layman, and because the effects of the disease are rarely serious enough to warrant recourse to professional advice. The pathology and histopathology of the papilloma of dogs and of cattle are well known. These tumours are characterised by primary multiplicity(14) and by a rate of growth which is often rapid, indeed parallel with that of malignant tumours; this is reflected by the high mitotic index which may be found in these growths (e.g. as much as 6 in the dog).

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(13) Probably because older animals have an acquired immunity to the disease.

(14) As distinguished from multiplicity by metastasis. It is likely however that often perhaps only one tumour is actually primary, the others being set up by contagion from this focus.

It has been said that papillomata are, for the purposes of this short discussion, to be treated as mixed (fibro-epithelial) proliferations. But in domestic animals all intergrades can be found from tumours in which the epithelial proliferation is preponderant to those in which the proliferation of the fibroblasts of the corium is the chief process concerned. The buccal papillomas of the dog offer the best example of the first type. These in their early stages consist in nothing more than a proliferated epidermis, which is thickened to form what is histologically a purely epithelial tumour, in the shape of a thick cap of epithelium without a stroma derived from the *cutis vera.* At a later stage the underlying connective-tissue elements start to proliferate, but only slowly, so that relatively highly collagenised neoplastic papillae of the corium result and one sees neither a great degree of cellularity of the fibrous tissue nor mitotic figures among the fibrocytes. In this later stage these tumours of the dog present what is usually accepted as the most typical picture of papilloma, and indeed these neoplasms have considerable claim to be regarded as purely epithelial tumours, the corium proliferation providing merely what amounts to a stroma, and being of no greater degree than is demanded for the support and nourishment of the

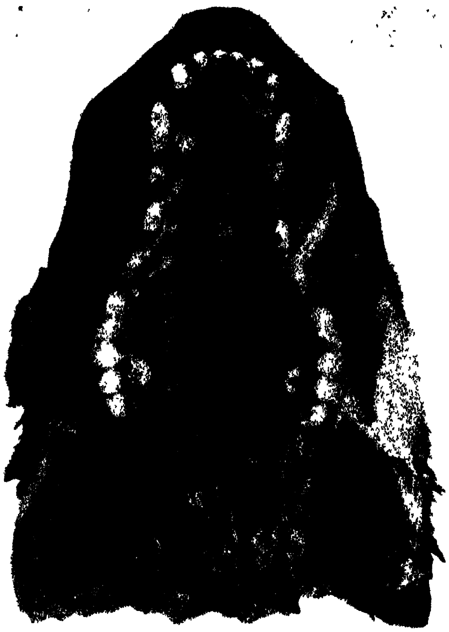

FIG. 174.—Contagious buccal papillomatosis of the dog: Cheeks, palate, and pharnyx affected. (14201; 1/2 ×).

neoplastic epithelium. These neoplasms of the dog usually remain small, for this very reason, although occasionally confluence of very numerous nodules in the fauces and pharynx may prove clinically a serious matter.

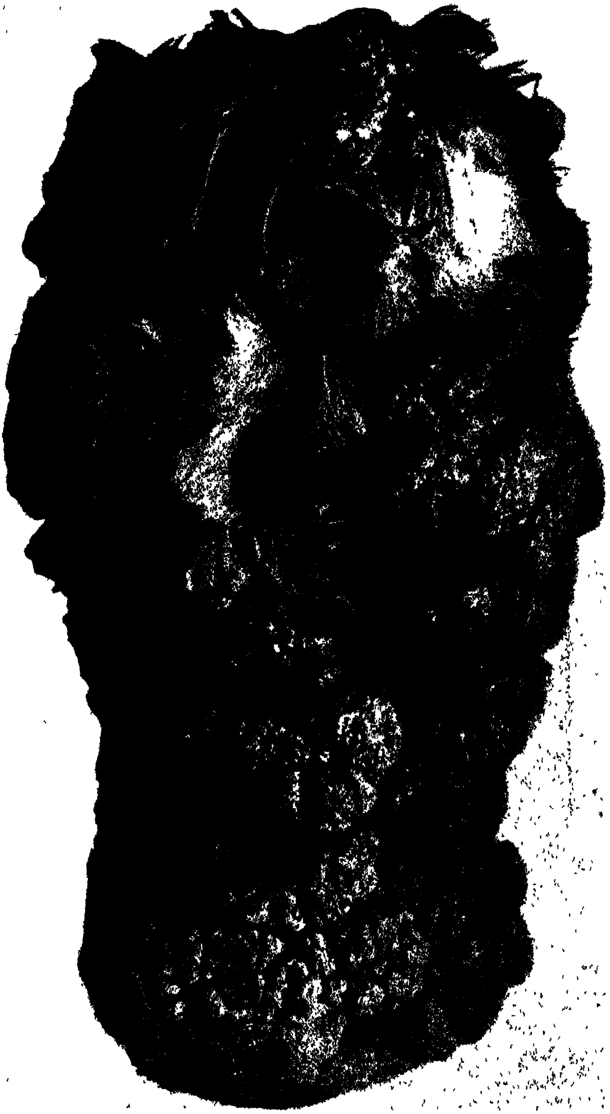

FIG 175.—A severe case of infectious papillomatosis affecting the head of a calf: Dorsal view of face. (4112).

In bovines a somewhat different picture is encountered. Here the tumours in question affect the skin. Again, in the most typical cases, the epithelial proliferation is preponderant, as may be seen even with the naked eye in the well known *papilloma coralliforme*, with its multiple acuminate, keratinized projections. But the elements of the *cutis vera* here play a less passive part: not only are the dermal papillae prominent and cellular—(fibroblasts), but the more superficial epithelial proliferation may rest on a veritable bed of proliferating fibroblasts which may extend into the subcutis, forming in itself a fairly circumscribed and discrete enlargement composed of cells which are proliferating with sufficient rapidity to preclude the deposition of collagen in any notable quantity. When such fibroblastic proliferation reaches its highest degree, it has been our experience that a diagnosis of " fibrosarcoma " or " spindle-celled sarcoma " is made, the superficial epithelial proliferation being referred to as an acanthosis and presumably being conceived as of the nature of a collateral or incidental hypertrophy of the epidermis. In these bovine tumours, generally speaking, epithelial and fibroblastic proliferation tend more or less to keep pace with each other, and histologically one has to deal with a mixed tumour, regarding which it may (although with doubtful profit) be argued which moiety undergoes the primary proliferation and which the merely responsive or secondary proliferation.

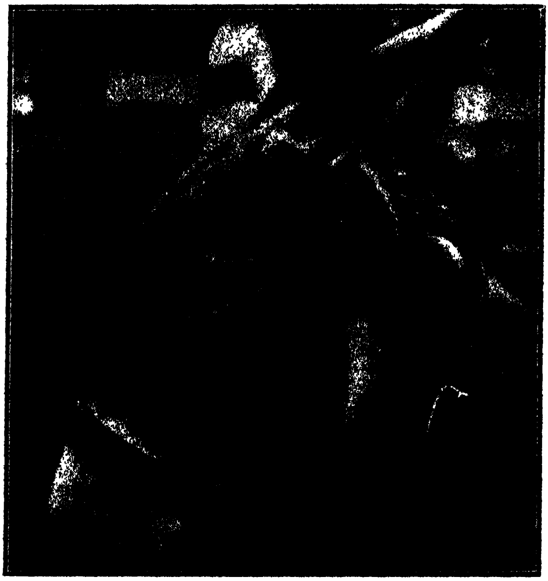

FIG. 176.—Typical fully developed sarcoid in a donkey. (Path. 17384).

In equines, tumours which are histologically obviously recognisable as papillomata are rare, in South Africa at least. On the other hand, we encountered no less than 44 tumours of the skin of equines (including horses, donkeys and mules) which had been variously diagnosed as "fibrosarcoma", "spindle-celled sarcoma", or "fibroma" of the skin, which were all clearly of the same nature, and which clinically have several features in common with tumours usually recognised as papillomata in other animals; viz. their tendency to multiple occurrence, their often rapid growth, and the evidence that they are transferred from one part of the body to another by contact. Their sites of predilection are the lower portions of the limbs (e.g. the cannon region), the eyelids, the lips, other parts of the skin of the head, and the sheath of the penis, etc. Clinically these tumours often appear to be transferred, e.g. from a limb to the lip, from the eyelid to a limb, from the sheath of the penis to the inner aspect of the thigh by direct contact of the parts such as occurs during biting, scratching, or during progression(¹⁵). Or they may be transferred to other parts (e.g. from one side of the head to the other) in a manner strongly suggesting the carrying of infection on the bridle, harness, or possibly the hands of attendants, etc.

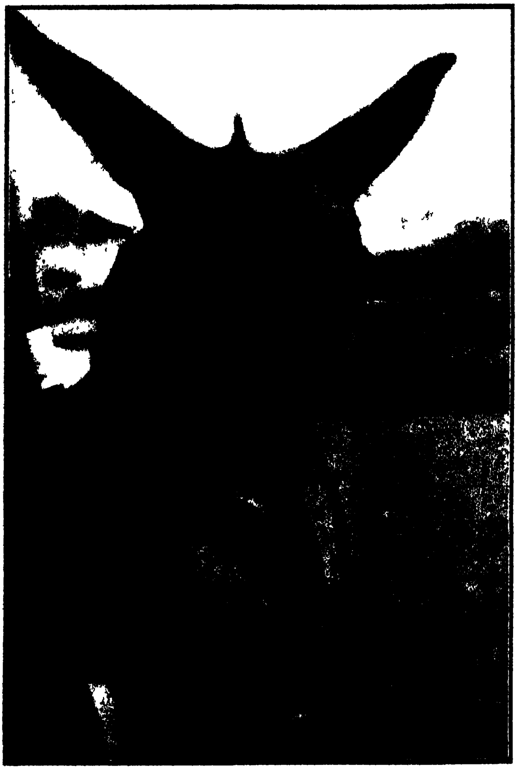

FIG. 177.—Front view of the head of the donkey shown in fig. 176: An early and not yet ulcerating sarcoid at the base of the right ear. (Path. 17384).

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(15) I am much indebted to Dr. J. Quinlan, Sub-Director of Veterinary Services, for his advice and information regarding the clinical behaviour of these tumours, of which he has had extensive experience in his surgical practice.

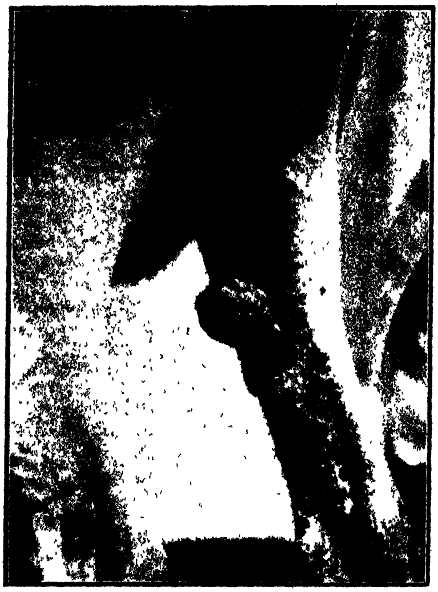

FIG. 178.—Another advanced sarcoid on the medial aspect of the crural region of the same donkey as figs. 176 and 177. (Path. 17384).

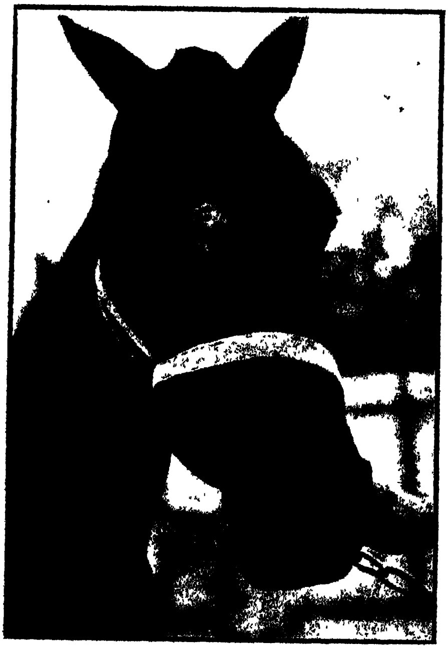

FIG. 179.—Sarcoid of the face of a horse: A case of recurrence after surgical removal. Photo taken about 6 months after operation. (D.O.B. 21276).

A study of this large series of tumours shows very convincingly their true nature. In the earliest stages (Fig. 181) they consist of a proliferation of the epidermis and a cellular proliferation of the cutis. At this stage the lesions may be recognised even with the naked eye as "papillomatous" because they are covered by acuminate keratinized epidermal processes, or at least by a thickened and "crusty" epidermis. But they are rarely seen or noticed in this form: soon the fibroblastic proliferation appears to gain the ascendancy and the neoplastic connective tissue early ulcerates through the epidermis. At this stage (Fig. 182), microscopically, one sees a cellular fibroblastic tissue which is covered only in part by what appears to be an acanthotic epidermis; the latter is thinning under the tension to which it is subjected from below, and in parts the fibroblastic tissue ulcerates through to the surface, becoming immediately the subject of a superficial bacterial infection with consequent leucocytic infiltration. In the later stages these tumours are no longer recognisable for what they really represent. They form, macroscopically (Figs. 176, 177, 178, 179, 180), bulky, pinkish-white, blood- and pus-encrusted, fungating outgrowths, overhanging the surrounding skin (which often shows smaller lesions of the same nature) and which show, when cut, a varying consistence: they may be fairly highly fibrous, especially in their deeper parts, or they may be softer, giving but little indication to the naked eye of any considerable degree of collagenization. They may be thickly pedunculated (Figs. 176, 177, 180) or more broadly attached (Figs. 178 and 179) to the skin. It

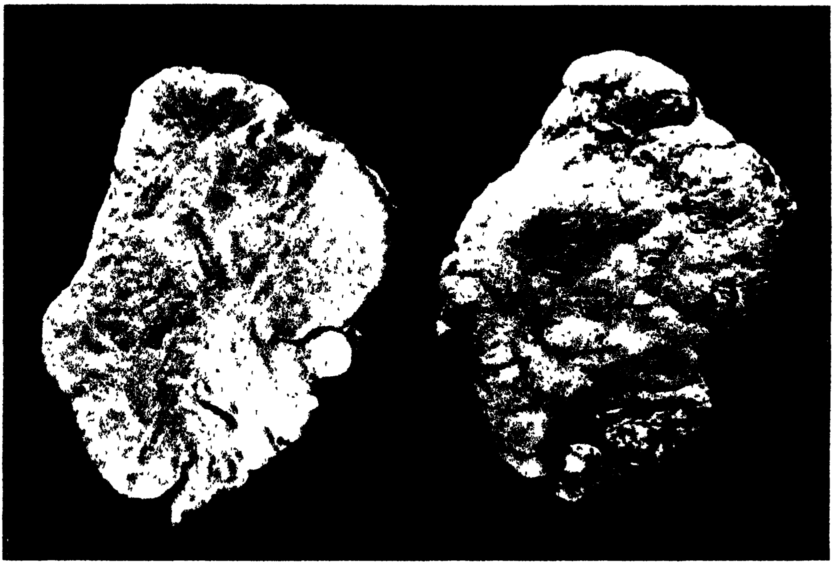

Fig. 180.—An equine sarcoid (from the skin of the leg of a horse) showing the ulcerating surface (right) and (left) the nature of the pedunculation on section. (16220; 3/5 ×).

is in this stage that the affected animals are almost invariably received for surgical attention, or that the specimen reaches the pathologist. The histological picture is as follows (Fig. 183):—

The growth consist of bundles of fibroblasts which are almost as irregularly arranged as in a sarcoma. They run in all directions. The degree of collagen deposition varies, being sometimes as much as to suggest the diagnosis of fibroma, or even of keloid, and being at other times almost absent, suggesting a diagnosis of "spindle-celled" sarcoma or at least of fibroplastic sarcoma. As in sarcomata, a greater or lesser degree of participation of the capillary endothelium is to be observed and occasionally mitoses can be seen in the endothelium of the budding vessels. This degree of capillary multiplication, however, is seldom sufficient to suggest the diagnosis granuloma, and indeed in virtue of its compactness and irregularity, and of the inconstancy of fluid or cellular exudate, the tissue could not be described as granulation tissue. Infiltrating neutrophils are constant only in the zone of ulceration. Infiltrating lymphocytes and eosinophiles are often more widely dispersed: the latter are a fairly constant feature of these tumours, but do not usually occur to the degree that is described in the lesions known as "summer sores"; they are often absent. In parts, areas of oedema may sometimes produce small foci of myxomatoid appearance. In the highly cellular tumours the mitotic index may be high, offering no chance of distinction from sarcoma. Yet apart from the often great irregularity of their arrangement, the fibroblasts show usually no distinct signs of anaplasia: gross irregularities of nuclear shape, hyperchromatosis, and nucleolar enlargement beyond the degree seen in non-neoplastic fibroblasts (e.g. in granulation tissue or in tissue culture) are not encountered. Only in a few cases were seen in tumours, otherwise identical with those being discussed, the intranuclear "inclusions" which have been referred to so often in this work. I did not consider that, on the grounds of their presence alone, a distinction should be made and a malignant tumour diagnosed. (It will be remembered that such inclusions are not confined to malignant tumours). The tumours do not invade deeply; and, although they are not encapsulated, muscle and bone are not infiltrated. In fairly advanced stages, fragments of the acanthotic epidemis with elongated rete pegs may be seen still adhering to the surface here and there.

A problem arises in the terminology of these tumours which is not easy to decide, and quite impossible of solution unless the whole process in all its stages, in its clinical features, and in its relation to the tumours of bovines and canines is kept in mind. At this Institute, many diagnoses of "granuloma" have been returned in respect of these growths. This is not admissible, for two reasons:—Although the tissue concerned may be conceived as being histologically intermediate between granulation tissue and (fibroplastic) sarcomatous tissue, it is nevertheless not granulation tissue histologically; secondly, the diagnosis of granuloma from biopsy material misleads the surgeon: these tumours are not readily amenable to surgical treatment; they have so notable a tendency to recurrence after extirpation (Fig. 179) that they appear to the clinician as

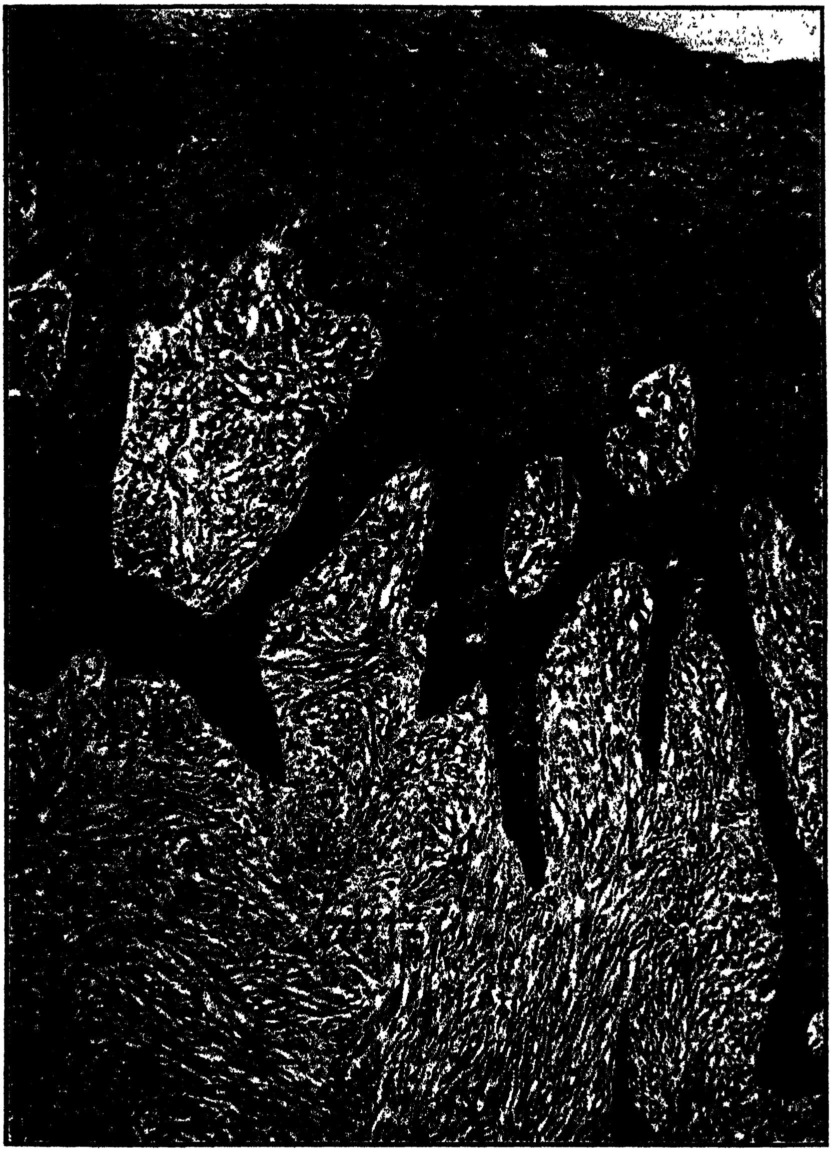

FIG. 181.—Structure of the equine sarcoid in the early stage: Acanthotic epidermis covering the proliferating dermal papillae (papillomatous structure). (16077; 120 ×).

actual (locally) malignant tumours. In a number of other cases, the equally unsatisfactory diagnosis of "fibrosarcoma" has been made. Here again there are several weighty objections: histologically those signs of cellular anaplasia which are associated with sarcomata are absent; unlike sarcomata, these tumours never give rise to metastases, or to deep invasion, and the unfavourable prognosis suggested by the diagnosis of sarcoma is therefore quite unjustified; lastly the extraordinarily high incidence of the growths is quite out of keeping with the comparative rarity of sarcoma (especially of the skin) in domesticated animals.

If, disregarding the histopathology of the tumour in its full developmental stage, and enthusiastic about those features of its inception and behaviour which point to a relationship to the contagious skin tumours of other species, we should call these tumours papillomata, there would no doubt be equally serious drawbacks: we are dealing with a process which, in its later stages, is a pure fibroblastic proliferation, very different from the classical picture of papilloma. Further, papillomata have come to be regarded as such innocent tumours(16) that a false optimism in respect of prognosis would be communicated to the clinician. Lastly, except in their earliest stages, the tumours bear little resemblance in gross pathology to papillomata.

In this quandary, I have been accustomed for some time past to return the diagnosis of "equine sarcoids" in respect of these growths. The term is adapted from human pathology. It is serviceable in expressing both the connective-tissue character of the growths and the caution which must be exercised from the prognostic standpoint. It denotes a process which is quite specific and further it relieves us from the responsibility of deciding whether these lesions are true tumours or more related to a chronic inflammatory process. The equine sarcoid is probably to be regarded as a one-sided development of papilloma. It may be that the cutis of the horse, as compared with other animals, responds more vigorously to the cause of papillomas than does the epidermis; or on the other hand we may regard the cause of these tumours itself to act for preference on the mesenchymal derivatives in equines and on the epithelium in dogs, the bovine occupying an intermediate position in this respect.

(16) As is well known, however, papillomatosis in calves may in individual cases be very serious in its results and neglected cases (Fig. 175) may carry unfavourable prognosis.

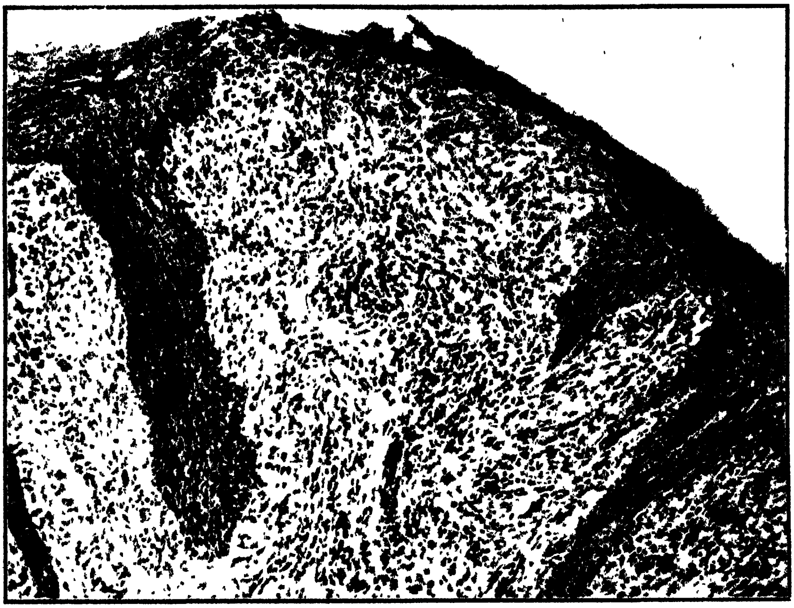

FIG. 182. A somewhat later stage in the development of equine sarcoid than was shown in fig. 179: the fibroblastic proliferation is "gaining the upper hand" and is commencing to ulcerate through the epidermis whose enlarged rete pegs are now undergoing atrophy. (14833; 90 ×).

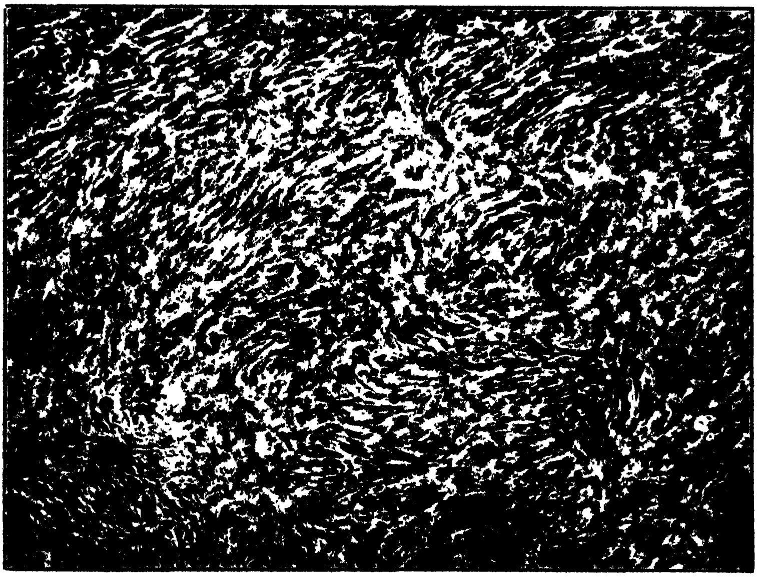

FIG. 183.—Detail of the structure of the fully-developed equine sarcoid: Irregularly disposed bundles of rapidly proliferating fibroblasts with moderate production of collagen. (2601; 175 ×).

CHAPTER XI.

The Contagious (Transmissible Venereal) Neoplasm of the Dog and the Heart-base Tumours of the Dog.

1. THE CONTAGIOUS (VENEREAL) TUMOUR.

General Considerations.

THE well-known contagious and experimentally transmissible canine neoplasms are unique in more than one respect. In the first place they are the only true neoplasms which are known habitually, and indeed (as we shall see) probably exclusively, to arise on the basis of transmission from individual to individual by direct contact and through an actual natural grafting of the neoplastic cells themselves. Secondly, they have consistently baffled attempts at a satisfactory classification on the basis of their histological characters, although an unlimited amount of material is available for study. It is true that the pathologist occasionally encounters examples of neoplastic processes to which it is difficult or impossible to assign a certain place in the histological classification, but this is usually because the rare occurrence of such processes precludes the obtaining of a large number of cases for study and comparison. Here, on the other hand, we have a tumour of common occurrence, cases of which can be produced at will with the greatest of ease; nevertheless, most cautious authorities are agreed that it is as yet unsafe to attempt the application of a rigid histological term whereby to describe them. While at first glance this may seem rather extraordinary and even an indictment of our ability as microscopists to reach a conclusion about the evaluation of the very definite appearances which are presented to us, yet a moment's reflection shows that the problem is a very real one, by no means to be solved by a mere unsupported assertion, on the part of any individual observer, regarding what he considers to be the histological and cytological nature of this tumour tissue.

Any microscopic diagnosis of a tumour, which is to be worthy of serious consideration, must be based on at least one, and preferably on both of two cardinal features: (*a*) the morphology of the cells, and (*b*) their histogenesis. Now it is in respect of these very two criteria that microscopic study has given so little assistance, (*a*) because the cells of this tumour remain in an undifferentiated state and neither by their actual structure nor by any structural products associated with their growth do they declare their nature; and (*b*) because, being transmitted from one animal to the next they do not in any given subject have an endogenous histogenesis; in other words they do not arise from the cells of the body of the affected individual. And when one considers that in spite of the association over some three decades of many greatly respected names with this morphological study, there is still to-day no agreement as to the cytological nature of these tumours, it is evident that anyone can scarcely hope, by purely histological study, to carry the problem further.

Earlier observers (e.g. Novinsky and Wehr) of these tumours considered them as carcinomas (i.e. postulated for the cells an epithelial nature). Later the pendulum swung in favour of "round-celled" sarcoma, or, more definitely, lymphosarcoma. To this view authorities of the repute of Beebe and Ewing (1906) and Sticker (1904) have subscribed, although the former make certain reservations. It will be recalled that Bashford and Murray's (1905) work was long responsible for an erroneous impression that the transmissible canine tumours were not true neoplasms, but infectious granulomas; and this was also the opinion of Wade (1908). Several workers since them, the first being Beebe and Ewing, have completely demolished the idea that the tumours did not grow by the multiplication of the (foreign) inoculated cells themselves, and to-day no one seriously questions the truly neoplastic nature of the process or believes that a virus, separable from the cells, plays any part in the appearance of these growths.

In spite of the reservations made by Beebe and Ewing regarding the lymphosarcomatous nature of these tumours, that view has been very generally, and in my opinion far too hurriedly, adopted. Histological examination favours, if anything, more their interpretation as carcinomas than as sarcomas. In favour of a carcinomatous nature is the alveolar structure (viz. cell-groups supported by a clearly distinct fibrous stroma) and the absence of intercellular fibrils; even the actual morphology of the cells themselves being at least as much in favour of their interpretation as undifferentiated epithelials as lymphocytic elements. In all these respects, so general a likeness to carcinoma do these tumours preserve that it has been found to be a fairly common error of diagnosis at this Institute to mistake them for basal-cell carcinomas (see Chapter II), especially when occurring in parts of the body where one does not expect to encounter "venereal" tumours.

There appears to exist a considerable misapprehension regarding the aetiology or pathogenesis of the "venereal" tumours. It is of course well known that in nature the great majority of these tumours occur on the genitalia (vagina, penis, prepuce, etc.). One finds it recognised occasionally in the literature that the tumours may occur elsewhere. Feldman (1932), for example, pictures a case where the head was affected, while Beebe and Ewing mention that "in both sexes isolated growths of the skin may occur . . . in the back, neck . . . or legs." But it appears to be very generally assumed that in such cases the appearance of the tumour is "spontaneous"—not by contagion—and indeed Beebe and Ewing categorically define the condition as "a venereal disease of dogs characterised by transmission through coitus . . ." Those who believe that transmission occurs solely through coitus and that growths (apart from the experimentally produced ones) occurring in parts of the body other than the genitalia must be explained as an actual "spontaneous" cancerization of (i.e. origin *de novo* from) the body cells of the affected animal itself appear to me to have gone astray in two respects. Firstly, due appreciation has not been accorded of the extraordinary ease with which these tumours may be transmitted, both by coitus and experimentally: on the genitalia, infection will take place in the absence of any visible defect in the mucosae; and, artificially, simple rubbing in of the tumour tissue on the scarified skin suffices. In consequence it appears *a priori* probable that coitus is not the only natural method of transmission, but that simple contact of an abraded surface, wherever it may be situated, with the tumour cells (such as may occur through biting, pawing, or perhaps even licking or lying on material contaminated with the tumour cells) may also cause infection. Indeed the fact that the tumours occasionally appear at sites remote from the genitalia is strongly in support of this view. What I wish to make clear, and what is nowhere in the literature lucidly laid down, is that there is no reason whatsoever to believe that all cases of the transmissible tumour, no matter where the lesions may be situated, are not due to contagion; and that there has been hitherto no satisfactory evidence in favour of the "spontaneous" occurrence of such a growth. On the principle *entia non sunt multiplicanda praeter necessitatem*, one must hold that the already established pathogenesis of the tumours by contagion throws so heavy a burden of proof on those who would assume, as a further cause, a "spontaneous" origin in some cases, that in the absence of any attempt to discharge this onus a multiplicity of causes does not merit serious consideration, least of all when such slender evidence is offered as (e.g.) that the subject of the supposed "spontaneous" tumour had not been known to have contact or coitus with a known infected animal. Feldman actually advances this as a reason for belief in spontaneous cases, disregarding the possibility that dogs may slip their chains unbeknown to their attendants and may also receive clandestine visitors into the hospitality of their own quarters. Three of the tumours in the Onderstepoort collection occurred at points remote from the genital organs, and in one of these cases a history of the development of the tumour at the site of a bite was definitely obtainable. It seems most likely that the majority of these cases are to be explained in a similar manner, the tumour cells being carried in the saliva and possibly on the ungulae. And, for any proof to the contrary yet offered, we must at present believe that all cases of this disease arise through cell continuity: the "cancerization" is an accomplished fact which need necessarily have occurred only on one single occasion, possibly at a very remote time, in a certain animal, of the body-cells of which all subsequent tumours are direct descendants. The fact that the tumours grow best in the dog and can be transmitted only to very nearly related species (the fox, according to Sticker) further allows us to assume that this act of cancerization actually occurred in a dog and not (as might otherwise have been a possibility) in some other species of animal.

The question now arises: Was this (hypothetical) instance of cancerization unique in canine pathology, or have we any other instances of it that may be observed? Hitherto there have been recorded no acceptable "spontaneous" tumours(¹) of dogs corresponding morphologically and biologically to the transmissible tumours. We have been fortunate enough, however, to encounter three cases of tumours in dogs in which the site and other features of the neoplasms completely excluded any but a "spontaneous" origin, and these are the heart-base tumours to be described. In morphology they are identical with the venereal tumours and a fragment of one of them, under the microscope, cannot in any way, even by the minutest study, be distinguished from the contagious tumours. It is regrettable that not one of these tumours was encountered unpreserved, so that the possibility (which I consider likely) of showing that this morphological identity is the reflection of a biological similarity could not be tested by transmission experiments with the heart-base tumours.

Occurrence and Pathological Anatomy.

The gross appearance of naturally-contracted transmissible tumours is well known to most veterinarians and this is one of the reasons why the number of cases (14) in the Onderstepoort collection cannot be assumed to be a true index of the frequency of this disease in South Africa. Many cases are diagnosed on clinical examination and a biopsy specimen is often not sent for microscopic examination prior to operation. This may well account also for the fact that such a high proportion of our cases did not occur on or near the genitalia; for it is from these very cases that specimens are likely to be submitted, most surgeons not being in the habit of suspecting contagious tumours in dogs when the lesions are not situated on or at least near the external genitalia, and having to resort to the aid of the pathologist in such cases. Of the fourteen cases of this disease which have been investigated, only nine were situated in the external genitalia, while the remaining four occurred as follows: elbow and (later) external ear; upper lip (extending to nostril); hip region; in one case the tumour was described as subcutaneous but the exact location was not stated by the sender. This distribution is amply sufficient to prove how essential it is, both for the pathologist and the surgeon, to be alive to the possibility of superficially situated tumours of the dog, no matter where they may occur, being of the contagious type. Failure to take this into account has resulted in unfavourable prognoses being given in respect of easily curable neoplasms.

The chief interest in this study has been found in a case of a simultaneous infection with the transmissible tumour and with actinomycosis; a case in which an extragenital tumour could definitely be traced to a bite; and the detailed observation on the cytology which have allowed us to correlate the contagious tumours morphologically with certain heart-base tumours of the dog. Only those which are essential to demonstrate these points will be reported here. Before describing the more atypical tumours, however, I shall give an example of the detailed observations on what may be regarded as a typical case.

(¹) No tumour situated at or near the surface of the body can merit consideration as "spontaneous" in view of the ease with which infection may occur.

Case 1 (*Canine*, 14931).

The relevant passages of the autopsy protocol on a male Maltese poodle, aged 8 years read as follows:—The scrotum is swollen, the skin being thin and shiny. There are two swellings related to the sides of but not involving the penis. On incision of the scrotum the testicles are seen to be displaced upwards by a mass of tissue attached to the scrotal skin. The internal iliac lymph gland is enlarged and hard, and on section of a denser consistency than normal. The superficial inguinal glands are hard, enlarged and on section of a whitish colour (causing the two swellings at the sides of the penis). Pathological-anatomical diagnosis; tumour of scrotum with metastasis to internal iliac and superficial inguinal lymph-glands. Aetiological diagnosis: destroyed owing to inoperable tumour metastases.

The specimen consists of the scrotum and testicles, the penis and sheath, and associated structures. The fundus of the scrotum shows a firm subcutaneous swelling covered by thin epidermis which in one part is eroded over an area of about 1 cm. On section the swelling is seen to be attached to the skin, not encapsulated but fairly well circumscribed. It displaces the testicles somewhat dorsally, is oval in shape, measuring 4 x 3 x 2 cm. and occupying the whole width of the scrotum. The colour is a pinkish-yellowish-white and the tissue cuts easily, having a firm, gland-like consistence. It is demarcated from the *tunica vaginalis parietalis* by the scrotal fascia. Both superficial inguinal lymph-nodes are enlarged, measuring 4 and 3 cm. in length (right and left respectively). They are not adherent to the skin or surrounding structures.

Microscopically:—The primary tumour is not encapsulated. It lies for the most part subcutaneously and in part intracutaneously, being limited by the more superficial portion of the *cutis vera*; but in places it extends to within a very short distance of the *stratum basale* of the epidermis. Under low power it appears to consist of solid continuous masses of cells with here and there an inconspicuous trabecula of collagenous tissue. On higher magnification, the continuity of the parenchyma is seen to be interrupted at frequent intervals by very delicate strands of connective tissue which divide the cell masses into solid cylinders of irregular shape and size, often two to three cells in thickness, which appear in section as alveoli. These fine septa are rich in capillary blood-vessels.

The cells are closely-packed polyhedral elements having rather distinct cytoplasmic boundaries and a characteristically "undifferentiated" appearance. In general one receives the impression of considerable cell uniformity, the great majority of the elements measuring 8·4 to 9·8μ in diameter. They have central nuclei, of spherical or, more often, slightly ovoid shape, which average some 5·6μ in diameter; smaller ones may measure 4·2μ and larger ovoid ones 9·1 x 4·2μ, or larger spherical ones 7μ. The nuclei are bounded by a well-defined nuclear membrane appearing as a sharp and clear-cut line. The most typical ones present a delicate and fine chromatin network, of which the nodes are not prominent, being visible as fine granules. But hyperchromatosis is very common, even the majority of the nuclei being affected thereby; in such cases the nucleus is crowded with relatively coarse, angular particles of basichromatin, which may either be uniformly distributed or show a predilection for the zone adjacent to the nuclear membrane. A fair number of the nuclei exhibit irregularities of form, e.g. are indented, pyriform, loaf-shaped, irregularly triangular, or kidney-shaped. Bi-nucleate cells are occasionally seen; in this case the nuclei may be elongated (14μ) and present flattened apposed surfaces due to mutual adaptation. Rarely, quite irregular nuclei are found with serrated or toothed outline over part of the circumference. Usually one nucleolus is visible in section, but a fair proportion of the cells have two. The nucleolus is prominent in most of the cells and in many it is clearly enlarged. The larger ones vary between 1·5 and 2·8μ in diameter, the smaller ones approximately 1μ. Occasionally alterations in shape are seen (cigar- or sausage-shaped nucleoli, which may measure as much as 4·9μ in length). The largest n : N ratios are 1 : 7 to 1 : 16.

The nucleus, in its finer structure, reminds one much more of an epithelial than a " mesenchymal " type. In many respects the typical ones are not unlike those of the basal cell carcinoma as regards their chromatin pattern, standing in contrast with the amblychromatic nuclei of the fibroblast or endothelial cell as well as with the heavily chromatic lymphocyte nuclei. In general the tumour cell nuclei are to be described as of leptochromatic and only moderately trachychromatic type (except where hyperchromatosis occurs).

The cell cytoplasm has a slightly opaque appearance and stains with haemalum-eosin a light pink-mauve. Where the cells are closely packed, its boundaries are distinctly outlined, showing as fine, refractile, pink-staining lines. By careful focussing, a finely granular appearance of the cytoplasm is seen.

In parts of the tumour associated with a moderate to rather heavy infiltration of eosinophils and lymphocytes, the tumour cells show a variety of changes, some at least of which are undoubtedly significant of degeneration, pycnotic nuclei being frequent. The cells may show prominent large vacuoles, staining with Sudan III, and they appear much swollen and in consequence to be situated farther apart. Their cytoplasm often shows a distinct, finely granular appearance—these granules being closely packed, staining with haemalum-eosin a light mauve and having a " soft " appearance; they may even be enlarged to a size comparable with that of the granulations of a neutrophile leucocyte and stain almost as bright a pink with haemalin-eosin; or although enlarged they may remain mauve-staining, but often take on a " harder " appearance than has been described. These granulations are not to be confused with those of the mast cells which are in evidence as an infiltrate, especially as the overlying epidermis is approached (these cells have much more closely-packed and intensely dark-purple-staining granules, which are usually arranged in the cell so as to leave a clear perinuclear zone). In the tumour cells under discussion the nuclear membrane is thickened and crenated and there are moderate to pronounced pycnotic changes. Often there are seen the most extensive distortions of nuclear shape—lobation, angularities, fissures, etc.

Sections of the superficial inguinal lymph-glands show that the architecture of these organs is much modified owing to a wide distension of the sinusoidal channels by the tumour cells, which in parts lie loosely among the meshes of the sinusoidal reticulum and mixed with the lymphocytes and eosinophil granulocytes, or in other parts form a solid growth with newly acquired stroma. Among the tumour cells, greater anaplastic departures are encountered than in the primary. For example, one large cell had an oval nucleus measuring 14×9·8μ with two nucleoli, the larger of which measured 5·6×2·8μ—(n : N ratio = 1 : 4). The cortical lymphoid nodules persist and are invaded at their edges by the tumour cells. (Here opportunity is found to compare the neoplastic cells with the elements of the lymphocytic series, which is of interest in view of the theory that these tumours are lymphosarcomas: the heavily-staining small lymphocyte without visible nucleolus and the medium lymphocyte, with its almost equally pachychromatic and trachychromatic nucleus and inconspicuous nucleolus, present an entirely distinct appearance; while the "large lymphocytes" in staining reaction much resemble the fixed reticulum-cells (from which most consider them to be immediately derived), having markedly vesicular nuclei with a far less heavy chromatin granulation or network than the neoplastic cell nuclei, and nucleoli which do not approach in prominence those of the tumour cells). Associated with this invasion a fair number of plasma cells occur in the lymphoid nodules at the expanding margin of the tumour cells. The medullary zone of the gland is obliterated by a solid growth of the tumour cells associated with a connective-tissue stroma which is richer than in those parts of the primary which do not show an inflammatory infiltration; here there is also a leucocytic infiltration.

Remarks.—This tumour had previously been diagnosed as *carcinoma basocellulare*, but the cells are typical of the contagious tumours and a careful study of the basal cell tumours of the dog shows the following differences which may be useful as a guide to those who find difficulty in making such a differentiation in cases where the contagious tumour makes its appearance in unfamiliar locations:—(i) The basal cell tumours usually occur on the head, especially the face, of the dog, but may occur elsewhere (e.g. on the shoulder, according to Feldman); the greater number of the contagious tumours occur on the genitalia, but they may also occur anywhere on the body, including the head. (ii) In the basal-cell tumours the stroma is prominent, highly collagenous and dense, while in the contagious tumours it is typically delicate and highly vascular, but under certain conditions (especially when the tumour is growing in organising tissue following the injury through which the cells were inoculated) it may also be denser and even hyaline. (iii) Regarding the cells in the basal-cell tumours these are typically elongated and arranged in rows with the long axes vertical, their nuclei are usually very uniformly ovoid or even cigar-shaped; in the contagious tumours on the other hand the cells are usually arranged in solid alveoli or cylinders within which the elements have no particular pattern, or when they are arranged in narrow rows or strands no vertical polarity is apparent; in shape the cells are spherical or when closely packed polyhedral, their nuclei are rounded to moderately oval. (iv) A pronounced contrast occurs in the prominence of the nuclei in these two classes of tumours; in the basal-cell growths the nucleoli are of a very uniform size and the maximum n : N ratio is *ca.* 1 : 25, while in the contagious tumours the nucleoli are nearly always prominent, vary in both size and shape and often may be enlarged to give ratios as high as 1 : 7, or in some cases even 1 : 3 or 1 : 4.

Diagnosis.—Contagious (venereal) tumour of the scrotum with metastases to the superficial inguinal and internal iliac lymph-nodes.

Case 2 (*Canine*, 15722).

The subject was a bull-terrier, 5 years of age, which, during a dog-fight, sustained a number of wounds including one on the right hip. Some time subsequently veterinary advice was sought for a walnut-sized swelling which according to the owner had developed in this hip wound. This tumour was excised in March, 1934. In November of the same year the case was presented at the clinic at Onderstepoort, there being a recurrence of the tumour at the point of the right hip and clinical signs of metastases in the superficial inguinal and internal iliac lymph-nodes, on account of which destruction was advised.(²)

At autopsy a large, rounded, discoidal swelling was seen to be situated over the right *tuber coxae*, measuring 10 cm. in diameter. Its central part is hairless and shows an ulcerated area (2·5 × 1 cm.) with a sharp epidermal margin. The growth on section is seen to occupy mainly the subcutis, in which (deeply) it is partially encapsulated. The consistence is firm and the colour yellowish-white. Over the swelling the skin is raised *ca.* 1·5 cm. above the surrounding surface. The circumference of the tumour can be felt through the skin to be well defined. One of the internal iliac lymph-nodes is enlarged to a size of 9 × 4·5 × 4 cm.; on section no cortex and medulla are visible, but the whole organ is occupied by a whitish tissue of firm consistence (but less resistant than the primary) which distends the capsule of the node. Other glands of this group are similarly affected, but less markedly enlarged. The superficial inguinal gland of the right side presents a similar appearance and is much enlarged.

Microscopically, sections of the hip tumour show that this is situated in the subcutis and is for the most part limited superficially by the deeper portion of the *cutis vera*, which however it invades at different points to reach the surface. There is a prominent stroma of connective tissue which is largely of a dense and hyaline nature, staining palely with van Gieson, but in other parts being fibrillar and fairly cellular. This stroma encloses strands of cells sometimes

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(²) I am much indebted to the Government Veterinary Officer, De Aar, and to the owner, Adolph A'Slaksen, Esq., for having taken some pains in replying to a correspondence whereby this history was elucidated. It is only fair to state that the Veterinary Officer's original impression was that the animal was suffering from a tumour which had been wounded, not a wound in which a tumour developed subsequently. Mr. A'Slaksen's subsequent explanation that immediately prior to consulting the veterinary officer, his dog (described as a great fighter!) had had another encounter, during which further wounds, including one in the immediate neighbourhood of the tumour, were inflicted, completely explained this misunderstanding.

lying in a single row or otherwise forming broader tracts of as much as a dozen cells in thickness. These cells are striking for their anaplasia and lack of differentiation. They are oval to rounded in shape where loosely packed, polyhedral where closely crowded, and vary in size from *ca.* 10μ to 66μ; the majority are medium-sized elements of some 14 to 20μ in diameter. They are characterised by an opaque, mauve-pink staining (haemalum-eosin) cytoplasm, which on the closest inspection is seen to be very finely granular or vacuolated. Especially in the larger cells, this cytoplasm tends to a more acidophilic reaction. In others of these cells the vacuolation may be more marked, conferring a distinct " honey-comb " or reticulated appearance on the whole or portions of the cytoplasm. There may also be larger vacuoles, varying in number from one to half-a-dozen, and one of these may occupy as much as half the area of the cytoplasm. Unexpectedly the fatty nature of these vacuoles could not be established by frozen sections. Typically the nuclei are irregularly spherical or slightly ovoid, but in a minority of cells there are marked departures from this shape. In the smaller cells they tend to be slightly eccentric, in the larger cells markedly so. They are characterised by a sharp, clearly defined nuclear membrane (which may often, however, be blurred or thickened on account of submembranal hyperchromatosis, the chromatin being prominent as a number of relatively coarse granules which are often more closely aggregated at the periphery of the nucleus, leaving a clear perinucleolar ring). Otherwise the nuclei have a rich but delicate chromatin network with just visible nodal points. There are from one to four very prominent (with haemalum-eosin) bright pink-mauve staining, slightly to markedly eccentric nucleoli. (Of these most nuclei have one, two are common, and three or four are seen in a minority of cases.) These nucleoli vary much in size but gross departures from a regularly spherical or oval shape are not encountered. The largest seen reached a diameter of over 16μ, and the n : N ratio in such cases may be 1 : 3. A fair number of the nuclei show distortion of shape and in some cases this is apparently related to the pressure of cytoplasmic vacuoles, causing the eccentric nucleus to assume a boomerang- or banana-shape. In multinucleate cells modifications of nuclear shape occur in adaptation to mutual pressure of the nuclei. Rarely, cells with exceedingly bizarre and lobated nuclei are to be found; such nuclei are pycnotic and the cells apparently degenerate. Multinucleated cells are fairly common but do not exceed in size the largest of the uninucleated elements. There may be considerable disparity, both as regards size and as regards anaplastic (especially hyperchromatic) changes, in the several nuclei of a bi- or multinucleate cell. Mitoses are frequent—(index 5). Both tripolar and tetrapolar divisions were seen.

There is throughout a moderate to fairly heavy infiltration of neutrophiles. These leucocytes may be found within the cytoplasm of the larger tumour cells. The stroma is richly vascular, both arterioles and venules being seen in considerable numbers in the hyalinised trabeculae. The relation to the latter of the tumour cells is often strikingly intimate, thin columns of the neoplastic elements appearing to be burrowing their way into the substance of the connective tissue. The strict absence of intercellular stroma is confirmed by the application of Mallory's triple stain.

The internal iliac lymph-node is almost completely replaced by neoplastic tissue, only occasional masses of the lymphoid tissue persisting. The detailed morphology is here much the same as in the primary, with the following exceptions: the stroma is less conspicuous, the connective-tissue trabulae being more delicate and hyaline changes being absent. Anaplastic changes, far from being increased, are if anything less marked: the extreme disparities in cell size are rarer and the cells do not reach at any time such gigantic dimensions. The other affected lymph-nodes show similar changes. All show neutrophile infiltration. Where lymphatics are seen they are almost filled with tumour cells mixed with these leucocytes. The histological findings in other organs are irrelevant. The adrenal of this subject contained multiple accessory nodules of cortical tissue.

Remarks.—From the diagnostic point of view this case presents obvious difficulties to those relying on the classical conception of the transmissible canine tumour as situated on the genitalia and microscopically showing a structure of "uniform small round cells". At first sight, it is likely that this tumour tissue, with its greatly developed stroma and whose cells present markedly hyperchromatic nuclei, very prominent nucleoli, great variation in size and bizarre nuclear forms might be mistaken for a highly undifferentiated carcinoma. Only a close study of the fine cell-morphology enables one with confidence to place this as a contagious tumour. These departures from the more typical morphology of the venereal tumours are doubtless to be explained by the fact that growth is taking place in a wound which is attempting to heal: the tumour cells are in fact growing in the scar tissue which is forming as a result of organisation; the hyalinised nature and great development of the stroma cannot to be explained on any other grounds when the rapid growth of the tumour (as confirmed both by the history and by the mitotic count) are taken into consideration. It is possible that this rapid growth has been further accelerated by the unsuccessful extirpation. What is still more interesting is that these anaplastic changes go hand in hand with the growth in the wound tissue, being less pronounced in the gland metastases, and thus forming an exception to the general rule that anaplasia is equally if not more pronounced in secondaries. Indeed the diagnosis is simple when the lymph-node tumours are examined and, on the contrary, by no means easy on the basis of the sections of the primary.

Diagnosis.—Transmissible (venereal) tumour affecting the subcutis of the hip region, developing as the result of a bite, and with metastases to the regional lymph-nodes.

Case 3 (*Canine*, 14826 *and* 15993).

This subject was a male Aberdeen terrier from which, at the age of seven months, an oval tumour (14826) was removed from the skin of the lateral aspect of the elbow, slightly proximal to the summit of the olecranon. This tumour measured 2 × 1 cm. and was raised about 1 cm. above the surrounding skin, presenting an ulcerating surface. It had no definite capsule, but moved freely with the skin over the underlying structures. It was of firm consistence and light colour. Some eleven months later (i.e. when the patient was eighteen months old) a nodule (15993) was removed from the external ear. This latter specimen consists of a portion of skin showing a small nodule, 7 × 4 × 4 mm., situated beneath the epidermis, not ulcerating, and without definite encapsulation.

Microscopically, the elbow tumour is seen to be supported in the *cutis vera* by strong bands of dense collagenous tissue which at the edges of the lesion are continuous with those of the derma. Over a narrow circumferential zone it is covered by epidermis. It consists of closely packed, polygonal cells whose outlines are rather distinct and which vary a good deal in size, averaging some 8μ. They have rounded to oval nuclei whose diameter varies (in section) from 3μ to 7μ. A minority of these nuclei depart from the typical shape and may be kidney-shaped, indented, boomerang-shaped, or S-shaped. In general they are characterised by a sharply defined nuclear membrane enclosing a delicate chromatin network which may even approach that of the vesicular nuclear type. There are one or two moderately distinct nucleoli which vary in size, some appearing distinctly large and being often oval or even rod-shaped instead of spherical; they tend to be moderately to markedly eccentric in location, even lying against the nuclear membrane. A fair number of the nuclei are hyperchromatic, this change being evenly distributed or confined to the zone beneath the nuclear membrane, leaving a clear perinucleolar area. The mitotic index is 6.

There is no intercellular stroma, but the more delicate bands of the stroma composed largely of capillaries give intimate support to small groups of cells. A distinctly alveolar pattern is not seen. The accessory epithelial structures of the skin (glands and hair-follicles) are surrounded by the tumour cells and appear to offer considerable resistance to invasion, having disappeared only in the central portion of the tumour. Deeply there is no encapsulation. Superficially there is ulceration through the epidermis, with a haemorrhagic and purulent exudate.

The ear nodule (15993) is covered by the raised epidermis and is situated in the *cutis vera*. It does not differ significantly in structure from the elbow tumour, except that mitoses are less frequent and the n : N ratio on average somewhat smaller. Although many delicate strands of vascular connective tissue run between irregular groups and columns of the neoplastic cells, the Mallory triple stain shows an absence of intercellular fibrils(³). For the most part the overlying epidermis is unaltered and the infiltration of the superficial part of the corium usually fades out before the basal layer is reached; here and there, however, invasion of the epidermis can be seen to be just commencing in minute areas where the *stratum basale* has disappeared or where all the layers except the *stratum corneum* have been replaced. In such regions, there are, superficially, neutrophile infiltration and small haemorrhages.

Remarks.—The elbow tumour originally was erroneously diagnosed as *carcinoma basocellulare*, a "venereal" tumour not being expected at this site. The recurrence of the disease in the ear is

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(³) With Mallory's staining method one must be careful not to confuse the distinctly outlined cell borders with such structures as fibrils.

doubtless to be explained as a fresh infection, for it is most unlikely that the result of contact with the first tumour (i.e. an auto-infection) would take so long to declare itself.

Diagnosis.—Transmissible (venereal) tumours affecting the skin of the elbow and the external ear.

Case 4 (*Canine*, 15601).

The lesion was sent in by Dr. G. Kind, of Johannesburg, as a tumour from a male Maltese poodle, 8 years of age. It had been removed from the upper lip and nostril. Macroscopically it is an oval tumour, 2·5 x 1·5 x 2 cm., at its base partially covered by skin, elsewhere presenting an ulcerating surface. It is, although not encapsulated, rather circumscribed, on section yellowish-white, and fairly soft in consistence.

Microscopically this tumour is seen to occupy the subcutis and consists of delicate connective-tissue trabeculae separating masses of rather loosely aggregated cells having a faintly-staining cytoplasm and of oval or polygonal outline; the cytoplasm may, in neutrophile-infiltrated areas contain a few small fatty vacuoles; the nuclei are large, spherical to slightly oval, and have distinct nuclear membranes. The chromatin is arranged in fine division to give a slightly vesicular appearance to the nucleus; but this is often modified by hyperchromatosis, when the chromatin granules become coarse and irregularly scattered. There are one, two, or three prominent nucleoli and in many cells there is a pronounced increase of the n : N ratio (from *ca.* 1 : 50 to *ca.* 1 : 3). Occasionally, extremely large nucleoli are encountered, usually associated with changes in their shape (e.g. oval) and with nuclear enlargement. Sometimes large, binucleate tumour cells occur, and there are fairly frequent nuclear degenerations, producing pictures of the old "cancer parasites". In parts, the tumour cells have a fairly distinct tendency to be arranged in linear rows between strands of proliferating connective tissue. The stroma is usually rich in small blood-vessels but in parts it is extensively hyalinised. Superficially there is an ulcerating surface composed of necrotic neutrophilic exudate overlying a zone of granulation tissue. The mitotic index is 7.

The neoplastic parenchyma shows, almost throughout, a diffuse infiltration of eosinophiles and also small lymphocytes, and in many places these infiltrating elements (associated with a few neutrophiles) are aggregated to form small purulent foci which may or may not be encapsulated by connective tissue. In the centres of such foci are typical ray-fungus colonies with prominent eosinophilic clubs arranged in astral formation.

Remarks.—The cytology and achitecture are typical of the contagious tumour of dogs. The interest of the case lies, firstly, in the situation at a point remote from the genitalia but favourable to the occurrence of accidental infection during the nuzzling of affected genital organs or through being bitten; and secondly in a coincident infection of the tumour tissue with actinomycosis. This disease, *per se*, is rare in dogs. Doubtless the ulcerating tumour surface provided an extremely favourable portal of entry for the organisms (e.g. from the grass, etc.) The animal made an uninterrupted recovery and there has been no recurrence of either infection.

Diagnosis.—Transmissible (venereal) tumour of the lip, which has become secondarily infected with actinomycosis.

Summary of the Observations on the Contagious Tumours of the Dog.

The first case to be described represented a typical one both in respect of situation on the external genitalia and of the histopathology, especially the cytology. The descriptions of the other typical cases are therefore not published here. From a consideration of these cases we have seen that some typical characteristics of these tumours, which will be referred to again later, are: the limited local invasive powers, even though a definite encapsulation is not present; the tendency to an alveolar arrangement of the cells, differing however from what is usually found in carcinoma by the extreme delicacy of the stroma; the nature of the tumour cells—a moderate degree of uniformity but with some noteworthy variations in cell and nuclear size. The cells are polyhedral in outline where closely packed, or rounded to slightly oval where more loosely aggregated. The cytoplasm is distinctly outlined and often contains small or sometimes considerably larger fatty vacuoles. The nucleus is more allied to an epithelial cell nucleus than to the nucleus of any mesenchymal derivative . One's impression is that the cells show no distinct morphological similarity to any element of the lymphocytic lineage. The dissimilarity from known lymphosarcomas is further seen in the absence of an intercellular fibrillar stroma (in my opinion a fatal objection to the idea of lymphocytic nature of the cells), the absence of an association with cells of the reticulum type, and the absence of any indication of the gradation (such as one expects to see in mammalian lymphoid tumours) between fixed elements and the various-sized free elements of the lymphocytic series. On the other hand the tumour is not identical with any form of epithelial neoplasm that one is familiar with and although it has been said that, in arrangement and morphology, the cells resemble epithelial more than mesenchymal derivatives, in neither of these respects are they typical of epithelial elements. One feels it to be *a priori* a likelihood that these tumours are neither carcinomas nor lymphosarcomas, but some other kind of tumour which has not yet come into consideration so far as an affinity to the contagious tumours of dogs is concerned. These points will be considered again after dealing with the heart-base tumours.

2. TUMOURS OF THE BASE OF THE HEART IN THE DOG.

Herzbasisgeschwulste have been described in the dog especially by Barth (1920), who has reviewed the literature. Tumours of this region are also known in other species (horse, ox, sheep, and fowl). A variety of different neoplasms are concerned and these are of no particular interest to us here. Lymphosarcomata of the heart are mentioned by Magnusson (1916B) in his extensive review of heart tumours of domesticated animals. A perusal of the description of the cases he quotes, as well as those in his own, leaves no doubt that these were genuine lymphosarcomas, intercellular reticulum being present in every case. When affecting the heart-base they were considered to arise from the neighbouring (bronchial) lymph-nodes. It does not appear that in any case the tumour had the histology of the three heart-base tumours which are in the Onderstepoort collection. In examining these I was impressed by a quite extraordinary resemblance of the neoplastic tissue to the contagious (venereal) tumours of the dog. Indeed, it is not possible to make a distinction between the two tumour tissues under the microscope. Regarding the possibility of whether similar tumours have been encountered by previous investigators, the cases of Magnusson have already been dismissed. Of two tumours which merit more serious consideration in respect of a possible identity with the South African cases, one is that described by Joest (1912): this neoplasm was diagnosed as of thymic origin (" adenoma ") although it was not situated in the cranial mediastinum (but in the cardiac mediastium, dorsal to the heart) and Hassall's corpuscles were not present. It is possible therefore that this tumour was not a thynoma (the author was by no means certain of his opinion), but whether it was at all similar to those we have encountered is difficult to say. The histological description does not indeed give any clear indication that this was the case. The second was reported by Wetzel (1902) and macroscopically appears to have been very similar to our cases. An intercellular stroma was demonstrated, however, and the diagnosis arrived at was " mixed-cell " sarcoma. Unfortunately no photomicrographs are published in this report, and one cannot therefore be certain of the correctness of the diagnosis.

The material that I have investigated consists of two tumours situated at the heart-base of dogs, and a third which was submitted as having been removed from " within the thorax " at autopsy; the exact location was not stated, but its morphological identity with the other two tumours, as well as other common pathological features, allows one to assume with reasonable certainty that it was similarly located.

Case 1 (*Canine*, 7808).

This dog was an Alsatian wolf-hound which was also the subject of the embryonal epulis (a mixed tumour of the lower gum with pulmonary metastases) which was described in Chapter X. The tumour which concerns us here was an unrelated (primary) neoplasm affecting the heart-base (Fig. 184). Attached to the base of the heart, immediately caudal to the aorta and pulmonary artery and overlying the right atrium (on which it causes a marked concavity and which it compresses), is an irregularly spherical mass measuring 4·5 cm. (cranio-caudally) × 4 cm. (from side to side) × 3 cm. (dorsoventrally). It has a thin capsular investment under which the surface presents rounded bulgings up to 1·5 cm. in diameter. The pulmonary artery is accommodated in a groove on the cranial aspect of the tumour, which closely surrounds the caudal and lateral aspects of the wall of this vessel. On section of the tumour, delicate strands of connective tissue can be seen to penetrate inwards from the capsule into the greyish (preserved!) parenchyma, large areas of which have a lighter and somewhat opaque appearance (necrosis?).

Microscopically the tumour is seen to be covered by the epicardium, and beneath the serosal cells there is a thin encapsulation by collagenous connective tissue. This tissue, however, shows invasion at many points. There is a rich system of delicate and highly vascular connective-tissue trabeculae separating islands and strands of the parenchyma, which is everywhere sharply distinct from the stroma (Fig. 186). Penetration of the neoplastic tissue into venules (which are very abundant in the stroma) can be seen, as well as tumour cells within the blood-stream. The neoplastic cells are clearly outlined and (usually) slightly polygonal elements which are usually closely in contact with their neighbours and between which no fibrillar stroma is present (Figs. 186, 187). They have a moderately large amount of cytoplasm, of which from one-half to one-third is occupied by the nucleus. The cytoplasm is fairly characteristic, having a distinctly but finely granular structure, and stains quite intensely with haemalum-eosin (a deep reddish mauve); on

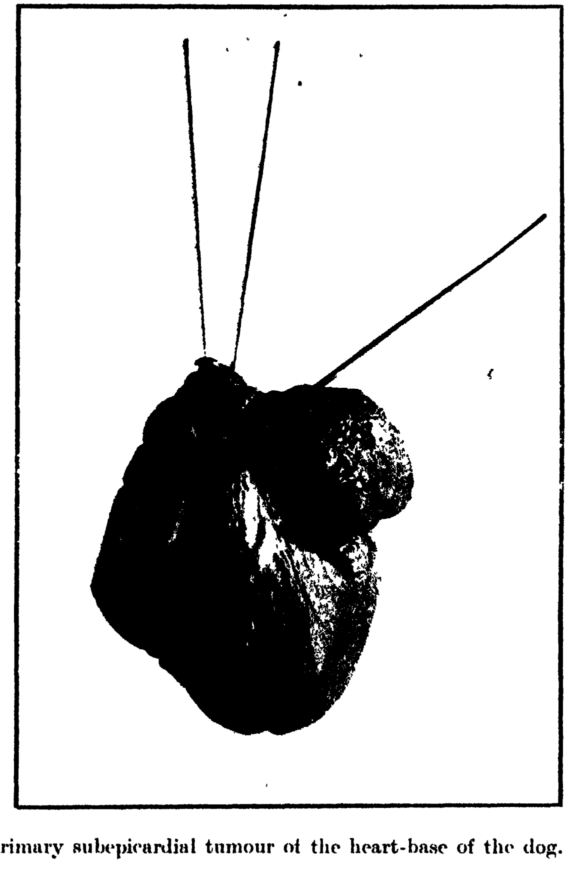

FIG. 184.—A primary subepicardial tumour of the heart-base of the dog. (7808; 1/2 ×)

account of the presence of these granulations it has a dense opaque appearance (not unlike that of a liver cell). The cells vary greatly in size from 11μ to *ca.* 70μ if the extremes are considered; but the great majority of them have a diameter ranging between 15 and 20μ. The large ("giant") tumour cells are scattered in a haphazard manner (Fig. 186) among the smaller elements or sometimes a group of several in fairly close proximity occurs (Fig. 187). Binucleate cells occur infrequently. The nuclei are most often centrally situated and conform in size to that of the cell, but occasionally a cell may show a tendency to a slightly elongated or columnar form, with the nucleus situated at one pole. The majority of nuclei are spherical to slightly ovoid, but many exceptions occur—pyriform, elongate-oval, bean-shaped, and occasionally very irregularly shaped nuclei are seen; the latter are usually associated with the very large cells. The more typical nuclei are moderately chromatic, showing a distinct meshwork or granular chromatin-content contrasting with

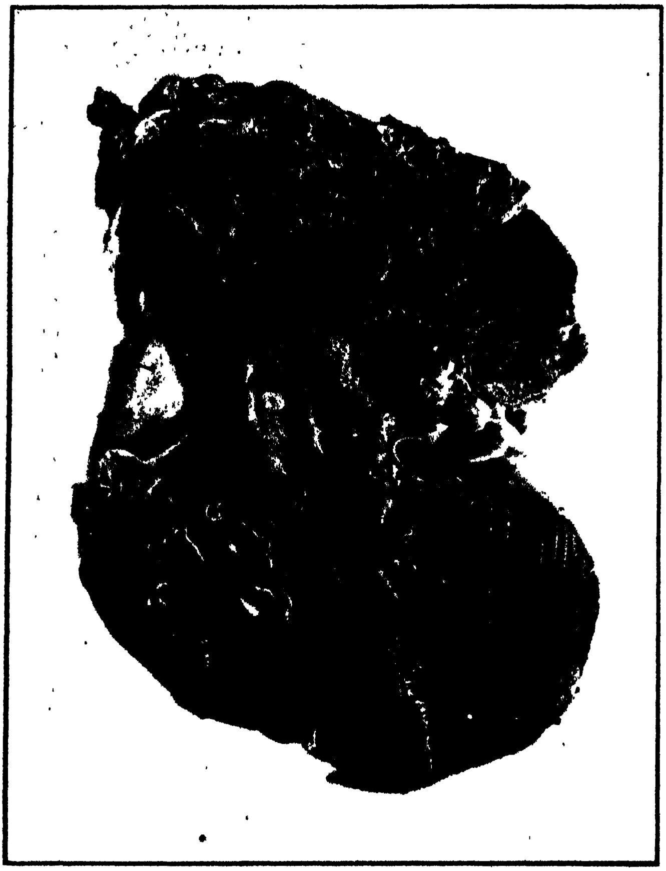

FIG. 185.—Another example of the primary heart-base tumour of the dog; note identical situation posterior to the root of the aorta and pulmonary artery. (15848; nat. size).

the clear nucleoplasm; actually, the majority of the nuclei depart from this arrangement on account of varying degrees of hyperchromatosis: many nuclei are heavily chromatic, containing many large and coarse granules, this being especially the case with the giant nuclei. In diameter the nuclei vary from some 8μ to over 50μ in the giant cells, the average size being *ca.* 10 to 12μ. The nucleoli are usually single and central, and they are distinct and acidophile. In most cells a n : N ratio of *ca.* 1 : 20 was recorded, but ratios of 1 : 10 are commonly seen and in the giant nuclei the nucleoli are proportionately enlarged (Fig. 187 below). Secondary changes occurring in the tumour tissue include extensive areas of total necrosis; in other parts only those tumour cells nearest the blood-vessels survive, producing a (spurious) peritheliomatous appearance. In other regions haemorrhages are frequent, as well as

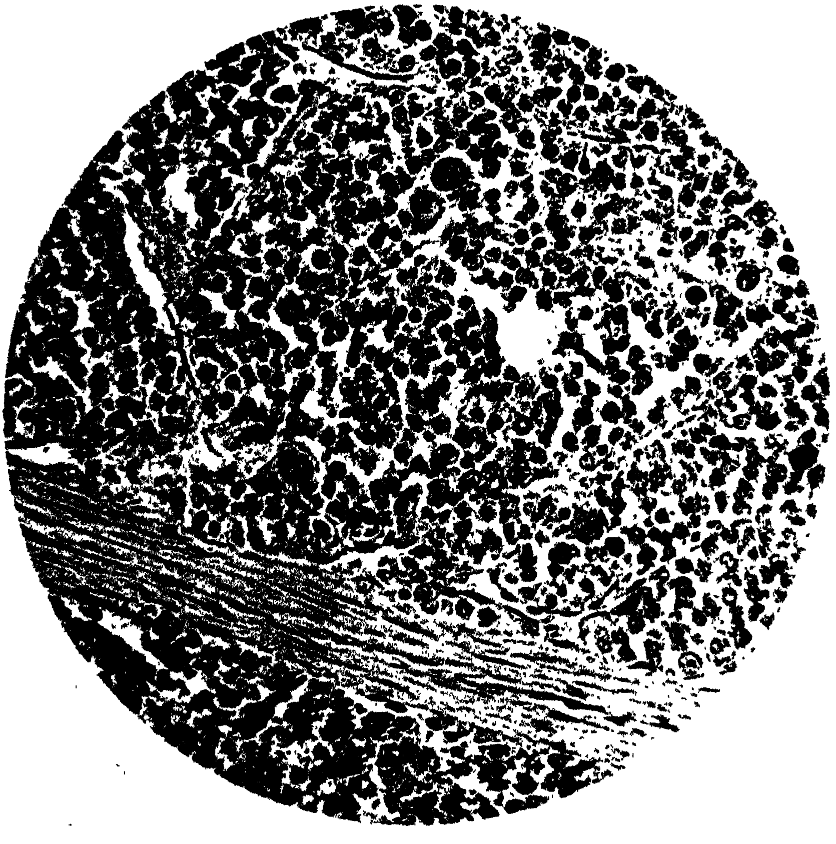

Fig. 186.—Structure of the heart-base tumour shown in fig. 184: Note identical structure to the well-known contagious venereal tumours of the dog; indifferent "round cells" grouped into alveolar units by delicate stromal strands; absence of intercellular stroma. (7808; 240 ×).

fresh blood-cells in direct contact with the tumour cells and possibly still in circulation, apparently occupying ill-defined channels between the neoplastic elements.

Remarks.—The independence of this heart-base tumour from the other primary tumour (of the gum) in this subject is shown by a total dissimilarity in the morphology, by the fact that the pulmonary metastases of that tumour (which would presumably be earlier established than metastases elsewhere) are small in size, and by our familiarity with the heart-base region as a site of primary neoplasms in the dog. The impression one gains of this tumour is that it is of epithelial rather than sarcomatous nature; and in view of the difficulty of explaining a primary epithelial tumour in this region, a close investigation was made of the possibility that the tumour might be secondary (although not secondary to the gum tumour). It is true that there exists no detailed autopsy proctocol, but the autopsy was performed by a specialist in pathology and we can be reasonably certain that no other primary tumour was missed. However, in order still further to exclude the possibly secondary nature of the neoplasm, i.e. that it might have developed in one of the bronchial lymph-nodes, the latter were all identified in the specimen and found to be intact, including the *lymphoglandula*

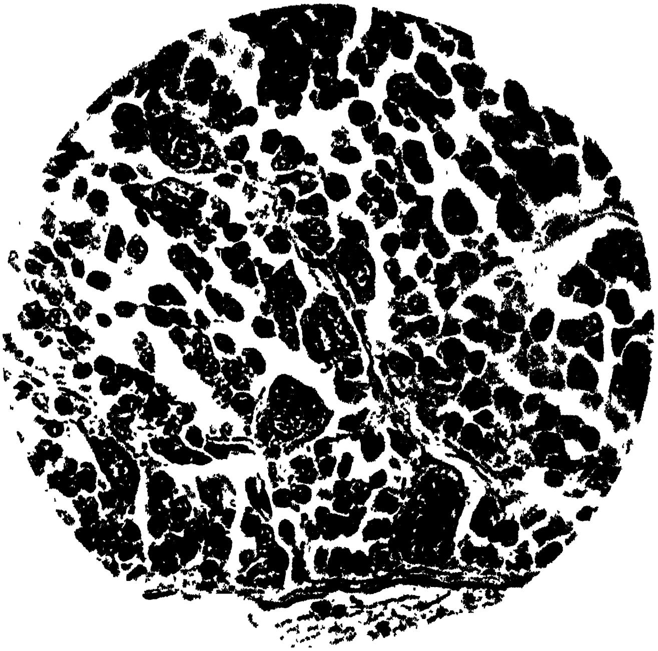

FIG. 187. —Higher magnification of the heart-base tumour shown in figs. 184 and 186: An anaplastic field has been selected to show the range of variation in cell size. (7808; 310 ×).

bifurcationis sinistra, which is the nearest to the root of the pulmonary artery. The further investigations which were undertaken in an attempt to decide the nature of this tumour will be mentioned when the other cases have been considered.

Provisional Diagnosis.—A primary heart-base tumour having a morphological similarity to the contagious (venereal) tumours of the dog.

Case 2 (Canine, 15848).

For this specimen I am indebted to the Officer in Charge of the Allerton Laboratory who informed me that it was taken, at autopsy, "from an aged Sealyham dog suffering from ascites . . . and a peculiar lesion at the base of the heart ". The heart (Fig. 185) bears a large, irregularly oval, flattened tumour lying on and firmly attached to its base, and measuring 7 x 4 x 3·5 cm. The heart and tumour together weigh 195 gm. The tumour lies between the termination of the *venae cavae* on the right and the aorta on the left, and causes a considerable modification in the shape and extent of the left atrium; the auricle is compressed between the tumour above and the ventricle below, and it tip just reaches to the caudal border of the heart, being 2 cm. posterior and to the right of the commencement of the left longitudinal groove. The surface is rough and irregular and not enclosed by a distinct capsule. On section the tumour is found intimately to envelop the pulmonary artery, although it does not invade it (the artery actually passes through the cranial portion of the neoplastic mass). It also closely surrounds, on all sides except the left, the aortic arch, which occupies a deep fossa in the tumour tissue. The colour of the (preserved) tissue is a light yellowish-grey with many darker grey fields, as if necrotic. One can detect occasional thin trabeculae of connective tissue enclosing a softer parenchyma. The consistence is gland-like. Included in the specimen is also a smaller piece (3·5 x 3 x 1·75 cm.) of similar tissue which (on enquiry) was reported to have been a somewhat detached portion of the main tumour. The lungs are imperfectly collapsed and appear as if they had been oedematous prior to fixation. The cardiac lobe of the right lung has a solitary, subpleural, circumscribed, non-encapsulated, whitish focus, spherical in shape and measuring 3 cm. in diameter; it is slightly raised above the lung surface and deeply it extends into the pulmonary parenchyma. The bronchial lymph-nodes were all identified and found to be unaltered except for an anthracotic pigmentation. A portion of the post-cardiac oesophagus is included and shows a pronounced thickening of the wall (1 cm.). The liver is greatly enlarged and is modified in shape by multiple swellings producing a very bossellated surface: these areas, measuring several centimetres in diameter, appear to be produced by aggregations of poorly-defined, light-coloured foci varying from 0·5 to 4 m.m. in diameter, whose consistence is soft and friable. The rest of the hepatic tissue is darker in colour and shows numerous (reddish black) areas of haemorrhage. There are also a few scattered, encapsulated, rounded foci, 2 to 5 cm. in diameter and containing a (coagulated) jelly-like substance. The kidneys present the typical appearance of the common chronic nephritis in the dog (uneven surface, increased consistence, pale colour, small cysts in the cortex and in the medulla).

Microscopically: the heart-base tumour is seen to be partially enclosed in a thin collagenous capsule, but in other parts the surface is free. Thin branching trabeculae proceed inwards, incompletely demarcating the parenchyma into lobules or alveoli, which in any given part are often fairly uniform in size. From these primary trabeculae proceeds a rich system of secondary septa carrying capillary blood-vessels and demarcating the parenchyma of each lobule into small, solid, rounded alveoli or solid cylindrical branching cords. The neoplastic cells (Figs. 6 and 7) present the following appearance:—

They are rather large (average diameter some 15μ), closely-packed elements, having a dense cytoplasm which stains a deep mauve with haemalum-eosin and shows a finely granular or cloudy structure. The nuclei typically are spherical and centrally placed, but there are pronounced variations in nuclear size and shape, especially in certain fields: large oval nuclei are common, more than twice the size of the others. There also occur nuclei which are spindle-shaped, lobated, cuboidal, kidney-shaped, or angular. Bi- and trinucleated cells occur. The largest nuclei measured as much as 35μ in long diameter, the smallest 4·2μ to 7μ, and the average diameter was about 11μ. The more typical nuclei have a prominent and somewhat wide-meshed chromatin network which appears as if composed of branching chains of fine granules. Between these meshes the unstained nucleoplasm appears almost as vacuolations. A large proportion of the cells have hyperchromatic nuclei with richly and uniformly distributed coarser granules producing a trachychromatic appearance; or the granules may show varying degrees of predilection for the peripheral zone of the nucleus, in which case the nuclear membrane appears of exaggerated density; or when a wider peripheral zone is affected the nucleus may appear dark with a light, clear, central perinucleolar area. The smaller nuclei usually show a single, fairly eccentric, and rather prominent nucleolus having a diameter of from 1·4 to 2·1μ and staining the characteristic, opaque violet-brown with haemalum-eosin. Many nucleoli are quite clearly enlarged and may even reach a diameter of 11·2μ (e.g. in a nucleus measuring 18·3μ in diameter), so that n : N ratios of as much as 1 : 2·9 were recorded. These very large nucleoli often have an altered appearance; while frequently preserving more or less a roughly spherical shape, they tend to be slightly angular or polyhedral in outline, while some tend to be oblong. They are bounded by a sharp and distinct border which apparently results from the crowding back of the juxtanucleolar basichromatin. They stain much more lightly than the smaller nucleoli, being a faint pink with haemalum-eosin (Figs. 7 and 9). In the ordinary way, they would be taken for the class of bodies referred to as intranuclear inclusions and only a careful study demonstrates their nucleolar nature: this demonstration comprises the finding of intermediate grades between them and the typical nucleoli, both in respect of size and staining qualities. Many of the smaller nucleoli show a peculiar vacuolated appearance (cf. the appearance of a typical Negri body), and these vacuoles coalesce to produce a central rarefaction resulting in a ring-shaped nucleolus with a central refractile vacuole (Fig. 6). This vacuolation is obviously the first stage in the process which culminates in the formation of giant nucleoli with loss of staining affinity. One must not be misled into judging these bodies to be not of nucleolar origin, merely because they may be found in a nucleus together with a normal nucleolus—in this case the nucleus has multiple nucleoli and it is not uncommon to find the following arrangements of bodies within the nucleus: 1 " inclusion " plus 3 nucleoli, 1 " inclusion " plus 1 nucleolus, 2 " inclusions " plus 2 nucleoli. It will thus be observed that there is the tendency to maintain an even number of altered plus unaltered nucleoli; in fact an odd number was not encountered, except in the case of nuclei with a single " inclusion " or a single nucleolus respectively.

In parts there are small, fresh haemorrhages with well preserved blood-cells lying in irregular small channels bounded by the tumour cells. In places the stroma shows considerable haematogenous pigmentation (haemosiderin). Necrosis has overtaken much of the tumour tissue and such necrotic areas may be bordered by necrobiotic neoplastic alveoli in which the cells have darkly-staining, opaque, homogeneous cytoplasm and pycnotic nuclei. Especially near such areas, cytoplasmic " inclusions " may be seen in degenerating cells: these have a " bird's-eye " appearance and apparently represent degenerate nuclei (extreme marginal hyperchromatism of the nucleus, with central chromatolysis). These *cellular* inclusions should not be confused with the *nuclear* inclusions mentioned previously. The mitotic index is 4.

The lung contains a solitary, non-encapsulated metastatic nodule of similar tumour tissue, in the cells of which the intranuclear " inclusions " are well developed (Fig. 9). It is limited superficially by the pleura. The pulmonary blood-vessels contain large numbers of fat-globules. Sections of the oesphagus show that the thickening of the wall affects all the layers from the *propria mucosae* outwards: in the latter, the connective tissue is dense and thickened and the submucosal glands form a thicker layer than normal; the chief change, however, affects the muscularis, which is increased to about five times its normal thickness, both the circular and longitudinal layers being affected. The liver is affected by a pronounced blood-stasis, the capillaries being distended and the liver-cells greatly compressed and often wholly atrophic. There are extensive areas of complete disappearance of liver-cells and replacement by lagoons of blood. The remaining liver parenchyma is affected by fatty changes. The kidney shows the lesions of a chronic interstitial nephritis.

Remarks.—In this case also the primary nature of the heart-base tumour is supported by the identification of the unaltered bronchial lymph-nodes and by the much smaller size of its pulmonary metastasis. This tumour is in essentials identical with that described in Case 1, and in gross appearance and location this growth is especially similar to that specimen. It is probable that the hepatic enlargement, due to congestion causing atrophy and haemorrhage, is to be referred to the pressure of the neoplasm on the termination of the caudal vena cava. The oesophageal hypertrophy is more difficult to explain: it cannot be directly referred to a stenosis caused by the pressure of the tumour, because the tube was affected by hypertrophy caudal to the position at which the tumour would have come into relationship with it. It may be explained as the result of pressure by the enormously enlarged liver at the oesophageal notch, but this could not be confirmed in the absence of the gastric cardia from the specimen; on the other hand it is possible that the hypertrophy had no relationship, either immediate or remote, to the presence of the neoplasm.

Diagnosis.—Primary tumour of the heart-base resembling histologically the contagious (venereal) tumours of the dog, with metastasis to the lung. (Stasis-atrophy and haemorrhages in the liver and ascites, secondary to the congestion caused in the systemic venous system by the presence of the neoplasm; hypertrophy of the oesophagus; lipaemia and chronic nephritis.)

Case 3 (*Canine*, 11331).

There is no autopsy record of this case, of the subject of which no particulars are available. The specimen consists of an egg-sized tumour removed " from the thorax " and of the liver of a dog.

Microscopically, the tumour consists of a moderately developed connective-tissue stroma demarcating lobules of parenchyma which are further incompletely separated into nests or strands by secondary, delicate, and vascular collagenous strands. The tumour cells are not separated by intercellular stroma and are morphologically identical with those described in the previous two cases and with the cells of the " venereal " tumours of dogs. They are closely packed and polyhedral. Their nuclei vary considerably in size, the smallest being of the size of the nucleus of a small lymphocyte, the largest three or four times this size. They are rounded to slightly ovoid in shape, occasionally irregular or polyhedral. Most show one distinct nucleolus, a few two. Usually the nucleolus is placed eccentrically, sometimes markedly so, i.e. in contact with the nuclear membrane. An increase in n : N ratio is apparent in many. Hyperchromatosis of the nuclei is common, the membrane appearing thickened and the chromatin network replaced by heavy granules which may be arranged in clumps adhering to the nuclear membrane. A striking feature is the hollowing-out of the strands of neoplastic cells by blood-containing channels, which vary in diameter so that between the lumen on the one hand and the stromal trabeculae on the other from four layers to one layer of cells may intervene. There is no tendency for these cells bordering blood-channels to be flattened and this process is not to be interpreted (as was done at the routine examination) as a tendency to blood-vessel formation (i.e. endothelioma): it is merely the direct bordering of blood-spaces by tumour cells such as is commonly seen in certain sarcomata, a condition which is highly favourable to haematogenous metastasis. In addition, the venules of the stroma can be seen to contain free tumour cells floating in the blood. The mitotic index is 3.

The liver is affected by severe hyperaemia and atrophy of the parenchyma (stasis- or cyanotic atrophy).

Remarks.—From the facts that this tumour is identical in morphology with the two heart-base tumours of the dog previously described, that we know it was intrathoracic, and that the liver showed changes the result of interference with the heart or with the emptying of the systemic venous system, one may conclude almost with certainty that this was also a heart-base tumour.

Diagnosis.—A tumour having the morphology of the heart-base tumours and the contagious venereal tumours of the dog and probably situated at the base of the heart.

DISCUSSION OF THE NATURE AND PATHOLOGY OF THE HEART-BASE TUMOURS AND THEIR RELATION TO THE CONTAGIOUS (VENEREAL) NEOPLASMS.

If one wished to demonstrate to a histopathologist the structural similiarity of the described heart-base tumours to the venereal tumours, one would not have to labour one's case, but would rather challenge him to tell them apart under the microscope. The most striking of the common features are: the delicacy and vascularity of the stroma, especially the secondary trabeculae, demarcating solid nests or strands of cells which are usually closely packed and polygonal in shape, whose cytoplasm stains identically with haemalum-eosin and has a somewhat opaque appearance due to fine granulations; the character of the oval or rounded nucleus, its degree chromatism and dispersal of the chromatin, the usually single or double nucleolus which is prominent and very variable in location, the constant presence of nucleolar enlargement, often to a very high degree, in some of the cells; the tendency to necrosis and haemorrhage: the formation of blood-channels directly lined by the tumour cells. In addition there is the limited local invasiveness, i.e. a tendency often to encapsulation but with invasion of the capsule and also of the blood-vessels. Even the growth-rate, as measured by the mitotic count, is not dissimilar—[average of 11 cases of contagious tumours = 6·6, or of 10 cases (discarding one atypical case with an index of 15) = 5·8; average of 3 heart-base tumours = 3]. Possible distinctions which were considered were a slightly greater regularity of the stroma in the case of the heart-base tumours and the absence of vacuolation of their cell cytoplasm. But the contagious neoplasms vary widely in these respects and such very minor considerations could not be used as a basis of differentiation. I had previously been of opinion that the contagious tumours of dogs should not be considered as lymphosarcomas, for the reasons that have already been outlined and had considered that they were more closely related to a *carcinoma medullare* in structure (alveolar arrangement, clear separation of cells and stroma, lack of intercellular stroma, and a morphology of the cells not incompatible with the view that they are highly undifferentiated epithelial elements). When heart-base tumours, arising spontaneously, were encountered having an identical structure, the difficulty arose (if these were to be diagnosed as *carcinoma medullare*) of explaining the origin of a primary carcinoma of the heart (for the occurrence of three such tumours—in two of which an autopsy examination had been made and further the bronchial lymph-nodes excluded as the source of the neoplasms in the heart region—makes it beyond doubt that we have here to deal with primary tumours). Kitt (*Bd.* III, S. 92) says quite definitely: " Epithelialer Krebs kann sich nicht als primäre Neubildung am Herzer entwickeln, da hier kein epithelialer Mütterboden vorhanden ist; " this is also the teaching of most pathological texts which mention the matter, the diagnosis of " primary carcinoma of the heart " (which has occasionally been made in the literature) being considered unacceptable. It was the very hopelessness of this dilemma —the encountering of primary tumours which were believed to consist of some sort of cells related to epithelium—which led me to examine serial sections of canine embryo hearts in the hope that some clue to an unsuspected *Mütterboden* for these tumours might be encountered. In view of the location of the heart-base tumours studied [which according to the regional classification of heart tumours would be classed as subepicardial extrapericardial tumours(⁴)] behind and between the roots of the aorta and pulmonary artery, attention was concentrated in this examination on the region in question. It was found that in (e.g. 90 m.m. crown-rump length) canine foetuses there are constantly present in the mesenchyme in the caudal angle between these two vessels, and partly insinuated between them, well-defined groups of cells of epithelial appearance, which are enclosed by and well-demarcated from the surrounding mesenchyme in the form of small solid alveoli. These cells show a quite striking similarity to the cells of the heart-base tumours (and to those of the contagious tumours, therefore), having the same deeply-staining granular cytoplasm and completely lacking in intercellular fibrils. A tumour arising from such cells would inevitably assume the exact position and topographical relationships of these heart-base tumours: in fact, as has been indicated, the position where it might be expected to find a matrix from which such tumours could develop was previously predicted as being at this point. There is little doubt that these epithelioid cells of the subepicardial mesenchyme must have been the source of the heart-base tumours, although exact proof has admittedly still to be obtained. Regarding the nature of this matrix, one knows from the work of Wollard (1926)—in dogs as well as in other species—that these cells are neuroblasts (sympathogonias or early sympathoblasts) which constitute the primordia of the sympathetic ganglia in this region. It is of course well known that apolar neuroblasts (i.e. before they differentiate to the extent of producing neurofibrils) are cells of very indifferent appearance which could scarcely be identified on the basis of the morphological cytology alone. Bielchowsky (1932) speaks of their " lymphocyte-like character ", and Kuntz (1920) indicates that they " may be recognised among the mesenchymal cells by the slightly larger size and more intense staining reaction of their nuclei ". In other words, it is evident that on grounds of cytological morphology alone there is little that is characteristic about these very undifferentiated elements. In my opinion,

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(⁴) By this is indicated that the tumours, developing beneath the epicardium (in this case that portion of the epicardium which covers the roots of the great vessels just before it leaves them to be reflected as the " parietal " layer of the pericardium) invaginate the latter into the pericardial cavity, but remain extrapericardial in position, in just the same way as the lungs or abdominal organs are extrapleural or extraperitoneal in situation.

the likelihood that the heart-base tumours described are actually neuroblastomas or, in more exact terminology, sympathogoniomas has to be seriously considered. The final proof of this falls without the scope of this work and will necessitate considerable research as well as probably the awaiting of opportunities to examine still further cases of the tumours in question.

Should this theory be definitely established, it will carry with it the corollary, which may at first glance appear surprising, that the contagious venereal tumour is also a neuroblastoma and not a lymphosarcoma. But a little reflection will show that this is not so extraordinary. Firstly, the histological identification of the contagious tumours has always been unsatisfactory, in spite of the closest study over a period of very many years. It is *a priori* not improbable, therefore, that actually a tumour of a somewhat unfamiliar nature is concerned. Secondly, authorities have been at variance regarding the (round-cell) sarcomatous or epithelial nature of the tumour; morphologically the neuroblast fits in very well here between these two possibilities: its ectodermal derivation confers upon it epithelial characteristics and at an early stage its actual form is that of an indifferent " round cell "; but it will differ from a mesenchymal " round cell " or lymphocyte by not being associated with intercellular stroma, which is foreign to the orientation of cells preserving epithelial habitus. Thirdly, in view of the ease with which neuroblasts may be cultured and transplanted, the existence of a contagious neoplasm composed of such cells is not particularly surprising. Lastly, it is illuminating to read how, in human pathology, a number of tumours, for decades considered to be round-celled sarcomas, have now been found to represent, most probably, neuroblastomas. This reform is due to the work of Kretz (1902); and especially of Wright (1910), who concluded that a number of so-called " round-celled sarcomas " affecting many different parts of the body are of neuroblastic origin and actually consist of proliferations of sympathetic formative cells. According to Ewing, his conclusions have been fully justified. It need not then surprise us if any tumour enjoying the doubtful name of " round celled " sarcoma or considered as a sarcoma of indifferent cells, which, like those of the contagious canine tumours, cannot be satisfactorily identified by competent pathologists after years of study, should prove to be of neuroblastic origin. On the other hand, the work of Wright has actually made this a suspicion which may well be aroused in all cases of such obscure tumours.

If the contagious tumours should prove to be neuroblastomas, it would then appear exceedingly likely that the hypothetical first " spontaneous " case, which was mentioned at the outset of this chapter, was a heart-base tumour such as those we have described. I say this because similar tumours have not been encountered elsewhere in the dog. By what means such a heart-base tumour might have been transmitted by contact to the (hypothetical) canine which bore the " first generation " of the contagious tumour we need not here speculate. Suffice it to say that, as I indicated previously, this transmission need have occurred only on a single occasion in the history of the canine race; and if there is any difficulty in imagining how a heart-base tumour itself could have been the source of infection it may be remembered that such tumours produce haematogenous metastases, so that a secondary in the skin or other superficial and accessible portion of the body is quite a possibility. Even if we were sure of our pathological facts this would be sheer speculation, however. All that I have here been concerned with is to show that the train of events suggested is well within the bounds of possibility and that, indeed, the whole problem of the contagious new growths of dogs in one which, by its very peculiarities, seems to demand for its explanation a set of circumstances which may, being themselves somewhat unique, harmonise with the unique results which have followed their operation and which have been such a puzzle in pathology. Such a " working hypothesis " opens the possibility of an investigational attack upon new lines. Should such investigation disprove this tentative hypothesis, we need not be disappointed: we shall at least have extricated ourselves from a groove along which we have not made satisfactory progress; and we may possibly fall into a new one which will lead us the quicker to our destination.

SUMMARY.

Certain features of the pathological anatomy of the contagious (venereal) tumour of dogs, especially the cytology, have been considered in greater detail than in previous works. It is shown that these tumours occur, with considerably greater frequency than is generally recognised, on superficial parts of the body quite remote from the genitalia, in which situation they are often incorrectly diagnosed. It is not necessary to explain these as " spontaneous " tumours, in contrast with lesions which are acquired through (cell) contagion : the sites at which they occur and in one case the history of occurrence in a bite-wound, lead one, on the contrary, to believe that the act of coitus is not the only method whereby these extremely viable neoplastic cells may in nature be transferred from one animal to another. Neither is it necessary to suppose that the original " cancerization " in the body of a dog (whereby became established this strain of tumour cells which have subsequently been transmitted from dog to dog) occurred on more than one occasion in the history of the canine species. Hitherto, however, we have known of no " spontaneously " arising prototype of the contagious tumour in the dog. This gap in our knowledge is supplied by the occurrence of certain primary tumours of the heart-base which histologically are identical with the contagious tumours, even to the finest details of their cellular architecture,(⁵) and which very probably are neuroblastomas, or, more precisely, sympathogoniomas, but of which further investigation is required both to prove their histogenesis more fully and to ascertain whether their resemblance to venereal tumours is not confined to the morphological aspect but extends also to a biological identity (viz. transmissibility). Although many years might elapse before one is fortunate enough to encounter a specimen of such a tumour under conditions in which transmission may be attempted, the occurrence of such an opportunity may be hastened if

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(⁵) It must be admitted that in the contagious tumours hyalinised nucleoli were not encountered, but this is an inconstant feature in the heart-base tumours.

veterinarians are made aware of the desirability of investigating suspected cases of heart-base tumours in the dog (symptoms of ascites and hepatic enlargement due to venous blood-stasis, etc.) with a view to supplying fresh tumour tissue for transmission tests.

In the consideration of the histopathology of these tumours, emphasis is laid on the high degree of cellular anaplasia which may be encountered, as opposed to the usually accepted conception of a cellular " monotony " of the contagious tumours, and observations are made on the variation in cell size and shape, nuclear size and shape, and especially on the very constant presence of nucleolar enlargement (which, if further evidence were needed of the truly malignant neoplastic character of these growths, would be of significance in the assessment of their nature).

SUMMARY.

In a study of the large number of specimens (approximately 600) which constitute the Onderstepoort Collection of Neoplasms and which have been encountered among domesticated animals in South Africa during a period of some fifteen years, special attention has been devoted to the incidence of neoplastic diseases in this country, to the histological and cytological morphology, and to problems of diagnosis, classification, and nomenclature of tumours of animals.

While the better known (and therefore more easily diagnosed) tumours receive statistical mention only, a detailed morphological study has been made of certain classes of tumours regarding which difficulties in diagnosis and classification exist: these include especially the primary epithelial tumours of the liver (with special reference to the differential diagnosis between hepatocellular and cholangiocellular carcinomas), thymoma, mesothelioma, endothelioma, " mixed-celled " sarcoma of the fowl (with special reference to the nature and behaviour of the cells of this tumour), certain mixed neoplasms, the contagious (venereal) tumour of the dog and certain heart-base tumours of the same species.

The more general features of neoplastic pathology which have received attention include the following:—

Estimations of the mitotic indices of many tumours have been undertaken and the significance of these counts is discussed.

Extensive observations have been made on the nucleolar-nuclear ratios in the cells of various kinds of tumours. A rapid technique for the estimation of this ratio is described and the significance of increase in n : N ratio in the estimation of malignancy is discussed.

The existence in several kinds of tumours of animals (hepatocellular carcinoma, thymoma, neurofibroma, avian " mixed-celled " sarcoma, certain heart-base tumours of the dog, etc.) of hyaline intranuclear " inclusion-bodies " is recorded, and evidence is presented to show that these bodies are of nucleolar origin. The stages in their development, by a process of vacuolation and hyalinisation of the nucleolus, are described and illustrated, and the fallacy of excluding a nucleolar origin of intranuclear " inclusions " merely on the basis of their coexistence in a nucleus with " normal " nucleoli is pointed out.

In dealing with the intercellular matrices and stromae of different kinds of tumours, evidence is presented in favour of an intracytoplasmic formation of collagen in the cells of the histiocytic sarcomas and the embryonal nephromas of the bird. The association of neoplastic endothelial cells with the production of reticular fibrils and their ability to transform into fibroblasts is discussed. The formation by one and the same cell of keratin and collagen is described in an embryonal tumour of the dog. The question of secondary osteoplasia in the stroma of simple tumours and of essential osteoplasia and fibroplasia in the parenchyma of mixed tumours receives notice.

Among tumours recorded for the first time are the following:—Carcinoma of the small intestine and carcinoma of the pancreas in the sheep; thymoma in the goat; embryonal nephroma in the horse; gliomas of the brain of the fowl; cutaneous neurofibromatosis in the fowl; probable sympathogoniomas (neuroblastomas) of the base of the heart in the dog; (reticulo)-endothelioma of the liver and spleen of the sheep; pericardial mesothelioma in the horse; and myo-lipoma of the vagina of the bitch; while a peculiar embryonal epulis of the dog, an interesting mixed tumour (simulating splenic tissue and having also an adenomatoid moiety) affecting the lung of a sheep, and leiomyomatoid carcinomata of the female genital tract and of the pharynx of the fowl are also features of the collection.

Of tumours which, according to the literature, must be considered great rarities, the following are represented in the Onderstepoort Collection: (glandular) carcinoma of the stomach of the horse, mammary carcinoma of the mule; cholangiocellular carcinoma of the liver of the ox, and hepatocellular carcinoma of the liver of the fowl; lymphangiomas of the subcutis of the ox and the mule and also of the pleura of equines; lymphangioma, lymphangiogenous endothelioma and mesothelioma of the serous membranes of bovines.

In fowls and in sheep the occurrence is recorded of a type of epithelioma which combines the excessive keratinization of *cornu cutaneum* with the invasive growth of acanthoma. The reasons for the existence of this tumour in ruminants and birds and for its occurrence in certain sites are examined.

The significance, diagnosis, and classification of certain cutaneous and apparently contagious neoplasms which are exceedingly common among equines in South Africa have been studied. The term (equine) sarcoids is proposed for these lesions, which in certain respects seem to stand midway between granulomata and sarcomata. A study of their histology and histogenesis, together with clinical considerations, provides evidence that they are to be regarded as one-sided developments of the lesions which in other species (dog and ox) constitute the well-known contagious papillomatosis; and that the existence of these sarcoids is apparently to be ascribed to the excessive response of the corium as compared with the epidermis to the aetiological agent of this disease in equines; i.e. the fibroblastic proliferation gains the ascendency over the epithelial proliferation, instead of that balance being maintained between the two moieties which results in the development of the typical papilloma in other species.

Attention is drawn to the frequent occurrence of the contagious (venereal) neoplasm of dogs at sites remote from the genitalia. It is concluded that there is insufficient evidence to show that these tumours, no matter where they may occur on the surface of the body, are ever due to any cause but the actual inoculation of tumour cells by contact with another animal (direct or, possibly, indirect); in other words there has hitherto been no good evidence in favour of the "spontaneous" occurrence of such tumours. The assumption of a "spontaneous" occurrence is, however, obviously necessary to explain how this tumour originally came into existence. In this work, the morphological resemblance between certain primary heart-base tumours of the dog and the contagious tumours is considered so striking as to justify a strong suspicion that the former constitute the hitherto unidentified "spontaneous" prototype of the latter. The heart-base tumours in question are tentatively identified as sympathogoniomas (highly undifferentiated neuroblastomas arising from the sympathetic formative cells which constitute the primordia of the subepicardial sympathetic ganglia of the heart-base); this opinion carries with it the corollary that the transmissible "lymphosarcoma" has been erroneously assessed by histopathologists and is in reality probably an apolar neuroblastoma or sympathogonioma.

Regarding the incidence of tumours of domestic animals in South Africa, the collection reflects the following data in respect of the frequency with which the pathologist encounters neoplasia in the different species:—(1)

Equine: sarcoids of the skin, 37 per cent.; acanthoma, 21 per cent.; melanotic sarcoma, 16 per cent.; carcinoma, 4 per cent.; lipoma, 2·5 per cent.; (cortical) hypernephroma (benign) 2 per cent.; all other tumours encountered, less than 2 per cent. each.

Bovine: acanthoma, 23 per cent.; carcinoma, 17 per cent.; papilloma, 14 per cent.; neurofibroma, 8 per cent.; embryonal (teratoid) tumours, 5 per cent.; *cornu cutaneum*, transitional cell carcinoma, lipoma, fibroplastic sarcoma and thymoma, each 4 per cent.; endothelioma, 3 per cent.; all other tumours encountered, less than 2 per cent. each.

Ovine: carcinoma, 28 per cent.; acanthoma, 25 per cent.; lymphocytoma (or lymphosarcoma), 10 per cent.; embryonal (teratoid) tumours, 8 per cent.; thymoma, 5 per cent.; (cortical) hypernephroma (benign), 5 per cent.; all other tumours encountered, 2·5 per cent. each.

Caprine: acanthoma and melanotic epithelioma, 44 per cent. each; adenoid epithelioma, 4 per cent.; all other tumours encountered, 2 per cent. each.

Canine: contagious (venereal) tumour, 19 per cent.: acanthoma and basal-cell epithelioma, each 11 per cent.; embryonal (teratoid) tumours, 10 per cent.; carcinoma, 10 per cent.; melanoma, 7 per cent.; all other tumours encountered, each 5·5 per cent. or less.

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(1) In reading the following figures, it is necessary to observe that "carcinoma" includes only "gland cell" carcinomas (i.e. carcinomas in the narrower sense; acanthoma, basal-cell epithelioma, adenoid epitheliomas of malignant type, and also mixed tumours having a carcinomatoid moiety being recorded separately).

Poultry: lymphocytoma (lymphoid leucosis), 45 per cent.; (glandular) carcinoma, 22 per cent.; leiomyoma, 7 per cent.; " mixed-celled " sarcoma, 7 per cent.; fibroplastic sarcoma and teratoid (embryonal) tumours, each 3·5 per cent.; all other tumours encountered, each 2 per cent. or less.

Too few tumours of the pig and the cat have been encountered to allow figures to be given for these species.

The outstanding features of these statistics are the high incidence of the equine sarcoids; and of glandular carcinomas of the sheep (a species which has been thought to be almost immune from that disease), the great preponderance of malignant epithelial tumours of the skin over all other tumours of the goat, and the frequency of lymphocytoma in the fowl in South Africa. In addition, the relatively high frequency of incidence (in contrast to what one would expect from other stastistics) of thymoma in ruminants and basal-cell epithelioma in the dog is worthy of remark.

The wealth and variety of the Onderstepoort Collection is a tribute to the interest in neoplastic diseases which has been shown not only by fellow pathologists but also by veterinarians in general and even by laymen in this country. It is hoped that the annotated and classified specimens to which this work forms a guide will provide a sound basis on which may be undertaken further and much needed investigations into comparative oncology and related pathological problems as encountered in South Africa.

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APPENDIX A.

Species Incidence of Tumours in South Africa.

Equine (horse, mule and donkey): 119 tumours.

Papilloma or sarcoid, 44; acanthoma, 25; melanotic sarcoma, 19; gland-cell carcinoma, 5; lipoma, 3; cortical hypernephroma (benign), 2; mesothelioma, 2; myxoma, 2; osteoma, 2; lymphangioma, 2; endothelioma, 2 (lymphangiogenous, 1; and haemangiogenous, 1); teratoid or embryonal tumour, 2; basocellular epithelioma, 1; malignant cortical hypernephroma, 1; phaeochromocytoma, 1; fibroma, 1; chondroma, 1; fibroplastic sarcoma, 1; melanotic epithelioma, 1.

Ox: 108 tumours.

Acanthoma, 23; gland cell carcinoma, 19; papilloma, 15; false neuroma (neurofibroma), 9; teratoid or embryonal tumour, 5; cornu cutaneum, 4; transitional cell carcinoma, 4; lipoma, 4; fibroplastic sarcoma, 4; thymoma, 4; endothelioma, 3 (haemangiogenous, 2; lymphangiogenous, 1); benign cortical hypernephroma, 2; mesothelioma, 2; chondroma, 2; lymphangioma, 2; lymphocytoma, 2; malignant cortical hypernephroma, 1; phaeochromocytoma, 1; osteoma, 1; mixed-celled sarcoma, 1; myxoplastic sarcoma, 1; teratoma, 1.

Sheep: 39 tumours.

Gland cell carcinoma, 11; acanthoma, 10; lymphocytoma, 4; teratoid or embryonal tumour, 3; thymoma, 2; benign cortical hypernephroma, 2; cornu cutaneum, adenoid epithelioma, myxoma, lipoma, osteoma, fibroplastic sarcoma, haemangiogenous endothelioma (reticulo-endothelioma), 1 each.

Goat: 46 tumours.

Acanthoma, 20; melanotic epithelioma, 20; adenoid epithelioma, 2; thymoma, leiomyoma, collision tumour, papilloma, 1 each.

Pig: 4 tumours.

Melanotic sarcoma, 2; haemangiogenous endothelioma, 1; papilloma, 1.

Dog: 72 tumours.

Contagious (venereal) tumours, 14; acanthoma, 8; basocellular epithelioma, 8; teratoid or embryonal tumour, 7; gland cell carcinoma, 7; melanotic sarcoma, 5; adenoid epithelioma, 4; lymphocytoma, 4; heart-base tumour, 3; papilloma, 3; fibroplastic sarcoma, 2; haemangioma, 2; fibroma, lipoma, chondroplastic and osteoplastic sarcoma, lymphangiogenous endothelioma, leiomyosarcoma, 1 each.

Cat: 2 tumours.

Basocellular epithelioma, 1; osteoplastic and chondroplastic sarcoma, 1.

Poultry: 203 cases.

Lymphocytoma, 92; gland cell carcinoma, 45; leiomyoma, 15; "mixed-cell" (histiocytic and fibroplastic) sarcoma, 14; fibroplastic sarcoma, 7; teratoid or embryonal tumours, 7; erythroleucosis, 5; acanthoma, 3; myxoma, 2; glioma, 2; teratoma, 2; collision tumours, 2; fibroma, osteochondroma, false neuroma, myxoplastic sarcoma, osteoplastic and chondroplastic sarcoma, myelocytoma, mixed leucosis, 1 each.

APPENDIX B.

ORGAN INCIDENCE OF PRIMARY TUMOURS.

Skin, Subcutis, Mucosae at Natural Orifices, and Tumours infiltrating the Pectoral Musculature of Fowls.

Cornu cutaneum: 3 bovines	3
Acanthoma: 62 equines, 1 bovine, 4 ovines, 18 caprines, 4 canines, 1 feline, 3 avians	93
Basocellular epithelioma: 1 equine, 8 canines	9
Adenoid epithelioma: 1 ovine, 2 caprines, 5 canines	8
Melanotic epithelioma: 2 equines, 19 caprines	21
Benign connective tissue tumours (including those of mixed type): 4 equines, 1 ovine, 1 canine	6
Fibroblastic and histocytic sarcoma: 1 equine, 1 bovine, 1 ovine, 1 canine, 3 porcines	7
Angioma: 1 equine, 1 bovine, 2 canines	3
Endothelioma: 1 porcine, 1 canine	2
Contagious (venereal) tumour: 4 canines	4
Papilloma or sarcoid: 41 equines, 11 bovines, 1 caprine	53
Lymphocytoma (see haemopoietic organs for skin leucotic tumours of avians).	
TOTAL	213

Digestive System.

(*a*) *Mouth.*

Acanthoma: 2 canines	2
Osteoma: 1 equine	1
Fibroplastic sarcoma: 1 bovine	1
Embryonal mixed tumour: 1 canine	1
Papillomata: 1 porcine, 3 canines	4
[*Tongue.*—Neurofibroma: 2 bovines (see nervous system).]	
TOTAL	9

(*b*) *Pharynx.*

Carcinoma leimyomatosum: 1 avian	1
Fibroplastic sarcoma: 1 bovine	1
Papilloma (1 case of canine buccal papillomatosis extended to the pharynx)	1
TOTAL	3

(*c*) *Oesophagus.*

Fibroplastic sarcoma: 1 canine	1
Histiocytic sarcoma: 1 avian	1
TOTAL	2

(*d*) *Forestomachs of ruminants.*

Acanthoma: 4 bovines, 1 ovine	5
Papilloma: 3 bovines	3
TOTAL	8

(*e*) *Stomach.*

Carcinoma: 1 equine	1

(*f*) *Intestine.*

Carcinoma: 1 equine, 1 avian	2

(*g*) *Anus* (*Anal glands*).

Carcinoma: 1 canine	1

(*h*) *Liver.*

Adenoma hepatocellulare: 2 porcines, 1 bovine	3
Carcinoma hepatocellulare: 6 bovines, 2 ovines, 2 mammals (species unknown), 1 avian	11
Carcinoma cholangiocellulare: 3 bovines, 1 canine	4
Endothelioma: 1 ovine (spleen also affected)	1
Lymphocytoma (see haemopoietic organs for hepatic lesions of avians).	
TOTAL	19

(*i*) *Pancreas.*

Adenoma: 1 bovine (multiple)	1
Carcinoma: 1 ovine	1
TOTAL	2

Respiratory System.

Nostril.

Fibroma: 1 equine (nasal polyp)	1

Paranasal sinuses (*including nasal chamber and ethmoidal muscosa*).

Transitional cell carcinoma: 2 bovines	2
Myxoplastic sarcoma: 1 bovine	1
TOTAL	3

Lung (*including intrapulmonary bronchi*).

Carcinoma: 1 ovine, 2 canines	3
Mixed tumours: 1 ovine	1
Lymphocytoma (apparently primary in lung): 5 avians	5
TOTAL	9

Circulatory System—Heart.

Endothelioma: 2 bovines	2
Heart-base tumours (sympathogoniomas): 3 canines	3
Neurofibroma: 1 bovine (see nervous system).	
TOTAL	5

Serous Membranes.

Peritoneum.

Mesothelioma: 2 bovines	2
Lymphangiogenous endothelioma: 1 bovine	1

Pleura.

Lymphangioma: 1 equine, 1 bovine	2
Mesothelioma (?): 1 equine	1

Pericardium.

Mesothelioma: 1 equine	1
TOTAL	7

Female Reproductive System (internal genitalia).

Carcinoma (including C. leiomyomatomasum): 22 avians	22
Leiomyoma: 15 avians	15
Histiocytic sarcoma: 4 avians	4
Myxoplastic sarcoma: 1 avian	1
Endothelioma: 1 equine (mule)	1
Teratoma: 1 equine, 1 avian	2
TOTAL	45

Female Reproductive System (external genitalia).

(For tumours of lips of vulva, see skin and natural orifices).

Vagina.

Mixed tumour (leiomyolipoma): 1 canine	1
Contagious (venereal) tumour: 2 canines	2
Leiomyoma malignum: 1 canine	1

Mammary gland.

Adenoma: 1 canine	1
Carcinoma: 1 equine (mule)	1
Mixed embryonal tumours: 5 canines	5
TOTAL	11

Male Reproductive System.

Testicle.

Carcinoma: 1 bovine, 1 canine	2
Teratoma: 1 avian	1
TOTAL	3

Prostate.

Carcinoma: 1 canine	1

Penis, Sheath and Scrotum. (For acanthoma, papilloma, sarcoid, etc., see skin and natural orifices).

Contagious venereal tumour: 7 canines	7

Nervous System.

Central nervous system.

2 gliomas of avians	2

Peripheral nervous system.

8 neurofibromas or neurosarcomas of bovines, 1 case of cutaneous neurofibromatosis of the fowl	9
TOTAL	11

Endocrine Organs.

Thyroid.

Adenoma or struma nodosum: 5 equines, 1 ovine	6
Lymphoid leucosis: 1 avian	1
TOTAL	7

Adrenal.

(*a*) Cortex: 3 equines, 2 bovines, 2 ovines	7
(*b*) Medulla: 1 equine, 2 bovines	3
TOTAL	10

Thymus.

Thymoma: 4 bovines, 2 ovines, 1 caprine	7

Urinary Organs.

Kidney.

Adenoma: 1 bovine	1
Carcinoma: 1 ovine	1
Embryonal nephroma: 2 equines, 5 bovines, 2 ovines, 6 avians	15
Lymphocytoma (lymphoid leucosis)—see haemopoietic organs for avian leucotic tumours).	
TOTAL	17

Bladder.

Leiomyoma: 1 caprine (multiple)	1

Haemopoietic Organs (including the skin, liver, and kidneys of fowls).

Lymphocytoma or lymphosarcoma (lymphoid aleucaemia): 88 avians, 3 bovines, 4 ovines, 3 canines	88
Myelocytoma: 1 avian	1
Erythroleucosis: 5 avians	5
Endothelioma: 1 ovine (spleen)	1
TOTAL	105

APPENDIX C.

CATALOGUE OF THE ONDERSTEPOORT COLLECTION OF NEOPLASMS.

Squamous Epithelial Tumours.

Cornu Cutaneum.

Bovine—10434, 12956, 15901, 16106	4
Ovine—6142	1
TOTAL	5

Acanthoma.

Equine.	
Conjunctiva or orbital region: 2393, 3577, 4698, 5351, 5740, 6123, 6250, 8745, 9233, 12515, 15312 (1), 16003	12
Penis or Prepuce: 2788, 3205, 4560, 8094, 9665, 14114, 16101, 16104	8
Groin: 10299, 11315	2
Site not stated: 2081, 2265	2
Secondary (peritoneum): 2593 (mule)	1
TOTAL	25
Bovine.	
Conjunctiva or Orbital Region: 5334, 5714, 6886, 7146, 7173, 8533, 10183, 12990, 13981	9
Rumen: 6054, 6055, 6060, 13627, 16158	5
Vulva: 2115, 15983	2
Skin (cheek): 5996	1
Site not stated: 2247	1
Secondary: 2753, 6052, 10718 (lymphnodes), 10488 (heart), 12952 (liver)	5
TOTAL	23
Ovine.	
Conjunctiva or Orbital Region: 7170 (2), 11859 (2) (=11625), 15277	3
Frontal or frontoparietal region: 6555 (3), 7576, 16300 (2) (3)	3
External Ear: 6262, 10742	2
Omasum: 13122	1
Site not stated: 10790	1
TOTAL	10
Caprine.	
Perineum: 7447, 7831 (4) (=7802), 8059 (4), 8483, 8639 (=9424), 8876, 9139, 9209, 9332, 9323, 9447, (=9647), 9448, 9675, 9939, 9970 (5), 10672, 15099	17
Face: 12306	1
Skin: 13814, 16239	2
TOTAL	20
Canine.	
Prepuce: 9744, 13575	2
Skin of other parts: 2345 (abdomen), 7417 (not stated), 15049 (=14976) (inguinal region), 15864 (scrotum)	4
Buccal mucosa: 7889 (hard palate), 15454 (2) (gums)	2
TOTAL	8
Avian.	
Skin: 10971 (3) (leg—metatarsus), 11984 (neck), 16236 (3) (leg—tarsus)	3
GRAND TOTAL	94

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(1) Denotes melanin-pigmented acanthoma.
(2) Denotes acanthoma with secondary osteoplasia.
(3) Denotes excessively keratinised acanthoma of the "malignant cornu cutaneum" type.
(4) Denotes lymph-gland metastases.
(5) Denotes lymph- and blood-borne metastases.

Basocellular Epithelioma.

Canine—6165, 7417, 10496, 11221, 14791, 14838, 15074, 15096	8
Equine—5918	1
Feline—14021	1
TOTAL	10

Adenoid Epithelioma.

Caprine—Perineum (sebaceous type) 8481, 8507	2
Ovine—Ear (E. adenoides cysticum) 9041	1
Canine—10223, 14838 (=14791), 15902(1), 15952	4
TOTAL.	

Glandular and Transitional(2) Epithelial Tumours.

Adenoma.

Equine—(Thyroid): 9616(3), 9276(4), 13077(4), 13413(5), 13449(6), 16203(4)	6
Bovine—2162(7) (pancreas), 5634(8) (kidney), 5640 (liver)	3
Porcine—(Liver): 6454(9), 6460(9)	2
Canine—5826 (testicle—"benign seminoma"), 16245 (male breast, A. fibrosum, "fibroadenoma")	2

NOTE.—For "sebaceous adenoma" see adenoid epithelioma. For adenoma of adrenal cortex see hypernephroma. For other adenomatoid lesions see "hyperplasias approaching neoplastic grade".

TOTAL	13

Transitional Cell Carcinoma.

Bovine—6224 (metastases in pharyngeal glands only), 17082 (do.), 13437, 16245.	4

Carcinoma (gland cell).

Equine—8099 (mule, mammary gland), 15193(10) (stomach), 2789 (mule), 4515, 11592 (mule, secondary: primary lesions not submitted)	5

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(1) Perianal sebaceous glands.

(2) That is, transitional between squamous and glandular epithelium.

(3) Spindle-celled type.

(4) "Foetal" (parenchymatous) and colloid type, with cyst-formation.

(5) Colloid and "foetal" or parenchymatous type.

(6) Solid "foetal" or parenchymatous type (almost exclusively).

(7) Multiple lesions, possibly classifiable as adenomatoid hyperplasia.

(8) Possibly to be regarded as a one-sided development of embryonal nephroma without invasive growth.

(9) Multiple hepatocellular proliferations, some of the nature of focal hyperplasias, others having progressed to small adenomas.

(10) With metastasis.

Bovine.

Liver (hepatocellular): 2121, 2669, 3224, 5608, 6072, 9729	6
Liver (cholangiocellular): 5771, 6278(1), 10764(2), 10765	4
Testicle: 6053	1
Secondary (primary not submitted): 2723 (lymph-node), 4897 (3) (lung and lymph-node) 9390 (liver), 13029 (liver) 13548 (liver and lung), 14555 (liver), 15915 (liver, lung and lymphnode)	7
TOTAL	18

Ovine.

Liver (hepatocellular): 13043, 13360, 16063	3
Other organs: 2611(1) (kidney), 4114 (small intestine), 6204(1), 6704(1) (pancreas), 11429 (kidney)(4), 15534 (lung)	6
Secondary (primary not submitted): 9470 (liver and lung), 11582 (liver)	2
TOTAL	11

Canine—3635 (5) (prostate), 6631 (lung), 10667 (anus—anal glands), 14319 (testicle), 14754 (6) (lung), 15152 (6) (liver—cholangiocellular), 16130 (7)	7
Mammalian (species not known): 3471 (1), 9810 (liver—hepatocellular)	2

Avian (i.e. fowls except where stated)—

Intestine: 14952 (8)	1
Liver (hepatocellular): 15815	1
Pharynx: 14035 (9)	1
Reproductive tract (female):	
(*a*) Ovary: 8289 (10), 8395 (9) (10), 8404 (10), 10338 (10) (11), 10619, 10620, 10709 (10), 11060, 12371 (10), 12660 (10), 13386 (10), 13525 (10), 13998 (10), 15018 (9) (10), 15359 (10), 15599 (10), 15814 (9) (10)	17
(*b*) Oviduct: 7746, 7747, 9313 (9) (10), 15844 (10)	4
Secondary (site of primary not recorded—implantation metastases on serosae): 8321, 8927, 8928, 8962, 9112, 9394 (12), 9873, 9874, 9892, 10143 (11), 10169, 10355, 10738, 11327, 12026, 12092, 12108, 14236, 14245 (9), 15650	20
Secondary (blood-borne): 4386 (turkey, liver)	1
TOTAL	45

TOTAL GLAND CELL CARCINOMA	88
TOTAL CARCINOMAS INCLUDING ACANTHOMA, BASAL CELL CARCINOMA, TRANSITIONAL CELL CARCINOMA, GLAND CELL CARCINOMA AND MELANOTIC EPITHELIOMA	196

(1) With metastases.
(2) Same subject had an acanthoma, secondary in lymph-nodes and probably primary in rumen.
(3) Included as secondary because of insufficient evidence of primary nature.
(4) Possibly a one-sided development of embryonal nephroma.
(5) With pulmonary metastases.
(6) With lymph- and blood-borne metastases.
(7) Lymph-node metastases only submitted.
(8) With metastases to liver.
(9) Carcinoma leiomyomatosum.
(10) With serosal implantations.
(11) Same subject had a leiomyoma of the oviduct.
(12) Parietal peritoneum also affected.

Hypernephroma.

(1) *Cortical Hypernephroma*—

(*a*) ***Benign type*** (" ***Adenoma*** ") :—

Equine—5570, 12575	2
Bovine—5925, 14336	2
Ovine—10054, 13867	2
TOTAL	6

(*b*) ***Malignant type*** (" ***Carcinoma*** ") :—

Equine—12614	1
Bovine—15514 [embryonal (false) mixed cortical tumour]	1
TOTAL	2
TOTAL (CORTICAL)	8

(2) *Phaeochromocytoma*—

Equine—13449	1
Bovine—8062	1
TOTAL	2

Mesothelioma.

Equine—9663 (=9383) (pericardial), 10423 (pleural)?	2
Bovine—6458, 12147 (both peritoneal)	2
TOTAL	4

Thymoma.

Bovine—5966, 6467, 12785, 14726	4
Ovine—2536, 13561	2
Caprine—12797	1
TOTAL.	

Benign Connective Tissue Tumours.

Fibroma.

Equine—15131 (nostril—F. molle et haemangiomatosum)	1
Canine—15904 (skin—umbilicus)	1
Avian—6893 (external ear)	1
TOTAL.	

Myxoma.

Equine—13599 (mule—subcutis), 13600 (mule—subcutis)	2
Ovine—14070 (neck—M. fibromatosum)	1
Avian—12659 (breast), 15063(¹) (wing)	2
TOTAL	5

(¹) Same subject had an osteochondroma of the dura mater.

Lipoma.

Equine—2803 (site not stated), 2887 (peritoneum), 4075 (mesentery).........	3
Bovine—3569 (omentum), 3627 (omentum), 6447 (thigh), 12748 (mesentery)...	4
Ovine—12688 (meniges—congenital)..	1
Canine—10345(1), (flank—multiple), 11328 (site not stated)................	2
Species not known—3437 (mesentery), 3618 (mesentery)......................	2
TOTAL........................	12

Chondroma.

Equine—9126 (external ear)..	1
Bovine—10752 (ribs), 14986 (sternum)......................................	2
TOTAL........................	3

Osteoma.

Equine—6136 (fascia lata), 11317 (osteoid osteoma, gum, mandible)..........	2
Bovine—4909 (cervical vertebrae)...	1
Ovine—8735 (mandible)..	1
TOTAL........................	4

Osteochondroma.

Avian—15063 (dura mater)	1

" *False Neuroma.*"

(Neurofibroma, neuromyxoma, neurosarcoma)—Connective-tissue tumours arising from the endo- (and peri-) neurium and closely related to fibroblastic tumours.

Bovine—

Brachial plexus: 10766 (2), 10828 (2), 13504 (heart also affected)............	3
Intercostal nerves (4): 13317...	1
Sciatic nerve (4): 12199 (2)..	1
Tongue: 6468 (2), 16258...	2
Site not stated: 10923 (3), 11769...	2
TOTAL (bovine)...................	9

Avian—

Cutaneous nerves: 8602 (multiple cutaneous neurofibromatosis or neuromyxomatosis)..	1
TOTAL........................	10

Malignant Connective Tissue Tumours.

Fibroplastic sarcoma.

Equine—4874 (mule, crural region)...	1
Bovine—7469 (heart—secondary ?), 10817 (shoulder), 12488 (=12585) (mouth), 13678 (pharynx)..	4
Ovine—7178 (hind limb)..	1
Canine—7414 (subcutis), 8550 (oesophagus) (5)..............................	2
Avian—7854 (site not stated), 10918 (site not stated), 10945 (5) (breast muscle), 10947 (subcutis, crop region), 11295 (lung, probably secondary), 12202 (secondary implantation intestine), 14442 (scapular region)............	7
TOTAL........................	15

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(1) Same subject had a mixed tumour of the breast.

(2) Intranuclear inclusions and a certain degree of cellular anaplasia present, possibly justifying a diagnosis of neurosarcoma, but definite invasive growth and metastases have never been seen.

(3) The same subject had a cholangiocellular carcinoma of the liver.

(4) The nerves affected are in these cases inferred from a description of the site and a knowledge of the predilection seats of the disease.

(5) With blood-borne metastases.

Histiocytic (mixed-celled) Sarcoma.

Avian—	
Ovary (with implantations): 8487, 10403 (1), 12007, 15100(2), 10918 (site not known—probably ovary)	5
Other organs: 8206 (oesophagus), 14117 (3) (wattle), 14508 (breast, pectoral musculature), 15433 (4) (abdominal wall)	4
Secondary lesions only submitted: 5128 (intestinal serosa), 11547 (intestinal implantations), 11987 (turkey—hepatic metastases), 13051 (hepatic metastases), 15161 (hepatic metastasis), 15427 (intestinal serosal and mesenteric implantations)	6
TOTAL—*Avian*	15
Bovine—6008 (uterus)	1
Ovine—8619 (hepatic and nephric metastases only)	1
TOTAL—*Mammalian*	2
TOTAL	17

Myxoplastic Sarcoma.

Bovine—11648 (paranasal sinuses)	1
Avian—12193 (ovary, with implantations)	1
TOTAL	2

Osteoplastic and Chondroplastic Sarcoma.

Canine—12754 (humerus—osteoplastic)	1
Feline—14067 (hock—osteoplastic)	1
Avian—9381 (bones, with metastases to muscles and subcutis—" osteo-chondro-fibrosarcoma ")	1
TOTAL	3

Angioma.

(1) *Haemangioma.*

Canine—15102 (skin, tibial region: H. cavernosum), 12062 (hip region H. cavernosum)	2

(2) *Lymphangioma.*

Equine—15537 (mule—flank: L. cavernosum), 8045 (pleura: L. simplex)	2
Bovine—3589 (pleura: L. simplex et cysticum multiplex), 12040 (site not recorded: L. cavernosum)	2
TOTAL—*Angiomata*	6

Endothelioma.

(1) *Haemangiogenous.*

Equine—14714 (subcutis, thigh: E. solidum)	1
Bovine—5144 (heart), 11070 (pulmonary semilunar valve)	2
Ovine—5847 (liver and spleen: reticulo-endothelioma)	1
Porcine—14967 (skin—multiple: E. haemangioplasticum)	1
TOTAL	5

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(1) With blood-borne metastases to kidney and musculature.

(2) Collision tumour with myelocytoma.

(3) With blood-borne metastases to spleen.

(4) With blood-borne metastases to liver, heart, kidney and lung, latter growing as myxosarcoma.

(2) *Lymphangiogenous.*

Equine—14924 (mule—ovaries with extensive peritoneal secondaries)........... 2
Bovine—8124 (*peritoneum*).. 1
Canine—9061 (*subcutis*).. 1

TOTAL........................ 3

TOTAL—*Endothelioma*............ 8

Leiomyoma.

Caprine—14142 (urinary bladder—multiple)................................ 1

Avian—

Oviduct or oviducal ligament: 4876, 7638 (1), 8844, 8869, 9712, 9986 (1), 9988 (1), 10093, 10143 (2), 10168 (1), 10298, 10338 (1), 10637, 14706 14
Ovary, also ovarian bursa and proctodeum (L. fibrosum—"fibroid"): 16058 (multiple).. 1

TOTAL........................ 16

Leiomyoma malignum (leiomyosarcoma).

Canine—16310 (vagina).. 1

Lymphocytoma.

(1) *Mammalian (Lymphosaracoma, lymphoid aleucaemia, "round celled sarcoma").*

Bovine—3180 (sternal region), 5124 (site not known)........................ 2
Ovine—5579 (lymph-node—site unrecorded), 6001 (caudal cervical lymph-nodes), 6816 (site unrecorded—subcutaneous), 9196 (cranial cervical—thyroid region).. 4
Canine—(lymphatic aleucaemia): 9592, 9964, 12019, 14733................ 4

TOTAL........................ 10

(2) *Avian (Lymphocytoma, lymphoblastoma, "round celled sarcoma," lymphoid leucosis).*

The following lesions are either situated in the cutis (and subcutis) or in the internal organs (especially liver, kidney, heart, etc.), or in both. They vary from discrete tumours apparently with blood-borne metastases ("round celled sarcomata") to a general affection of the haemopoietic system with formation of multiple focal infiltrations rather than actual "tumours.":—

Avian—

Fowl: 2818, 3633, 3904, 3905, 3978, 4727, 4923, 4992, 5129, 5940, 6093, 6204, 6369, 7196, 7197, 7226, 7354, 7362, 7535, 8063, 8064, 8074, 8090, 8122, 8354, 8462, 8522, 8731, 9310, 9367, 9449, 9464, 9552, 9554, 9762, 9792, 9838, 9839, 9840, 9987, 10017, 10173, 10351, 10352, 10358, 10369, 10520, 10436, 10523, 10569, 10635, 10723, 10818, 10864, 10914, 10919, 10942, 10943, 11052, 11194, 11283, 11428, 11722, 11802, 11873, 11882, 11919, 12114, 12021, 12186, 12379, 12801, 12922, 13145, 13195, 13214, 13793, 13794, 14062, 14540, 15117, 15235, 15496, 15522, 15525, 15646, 15962, 16159, 16259, 16320, 16321.................................... 91
Turkey: 11461.. 1

TOTAL........................ 92

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(1) L. haemangiomatosum.
(2) Same subject had transcoelomic implantations of a carcinoma of unrecorded site.

Myelocytoma (*myeloid leucosis*).

Avian—10918 and 15100 (collision tumours with ovarian histiocytic sarcoma) 2

Avian leucosis of mixed (*lymphoid and myeloid*) *type.*

Avian—9793 (lymphocytoma of oviduct and myelocytomatosis of liver)...... 1

Erythroleucosis.

Avian—8244, 8245, 9122, 11208, 15330.................................... 5

Glioma.

Avian—9805, 14258... 2

The contagious (*Venereal*) *Tumour of Dogs* (*Neuroblastoma ?*).

Affecting the male genitalia: 3301, 5918, 6098, 9181, 13918, 14931 (1), 14968 (1) 7

Affecting the female genitalia: 2790, 12316............................ 2

Affecting other parts of the body: 6803 (2) (subcutis, involving musculature), 9082 (site unrecorded), 14826 (=15993) (elbow and ear), 15601 (3) (lip and nostril), 15722 (1) (hip region)........................... 5

TOTAL.......................... 14

The Heart Base Tumour of Dogs (*Neuroblastoma ?*).

7808 (4), 11331 (cardiac situation inferred), 15848 (5)........................ 3

Melanin-pigmented Tumours of Epithelial Type (*excluding melanotic acanthoma*)—*melanotic epithelioma*, "*melanocarcinoma.*"

Equine—10187 (corneal conjunctiva)................................ 1

Feline—See basal-cell epitheliomas.

Caprine (all are tumours of the skin).

Perineum: 6189, 7256, 7481, 9168 (6), 9255, 9256 (6) (=9971), 9257, 13112 (6).. 8

Ear: 6999 (=7385), 9254, 9278 (7), 9425 (6) (=9586), 9585, 9787, 10235 7

Skin at base of horn: 6985 (7), 12004............................ 2

Skin at border of nostril: 16057............................... 1

Multiple primary tumours: 9258 (6) (=9963 (6) (perineum and ear), 12455 (perineum and foot)................................ 2

TOTAL *Caprine*................. 20

TOTAL.......................... 21

Melanin pigmented Tumours of Non-epithelial Type. (*Melanotic sarcoma, melanoma, melanoblastoma*).

Equine (8)—2376, 2823, 2863, 2992, 3148, 3338, 3421, 3440, 3990, 4064, 4068, 4854, 6095, 6959, 7748, 7951, 8530, 11319, 13501.................... 19

Porcine—10365 (skin, leg), 12896 (skin)............................... 2

Canine—9802 (=8658=10278, skin—forearm, groin), 10132 (skin—leg), 12846 (skin—interdigital space), 15432, (eyelid), 15715 (interdigital space).. 5

TOTAL.......................... 26

(1) With lymph-node metastases.

(2) With lymph-borne and blood-borne metastases.

(3) Tumour infected with actinomycosis.

(4) Same subject had an embryonal epulis (see mixed tumours).

(5) With pulmonary metastases.

(6) With lymph gland metastases.

(7) With lymph and blood-borne metastases.

(8) Many other such equine tumours were not kept as specimens although found at autopsy. Regarding the site there was too often an insufficiently complete examination to speak with certainty in many cases. But all are presumed to have been primary in the skin, that of the perineum and tail being well-known predilection sites.

Mixed Tumours.

(1) *Teratomata.*

Bovine—6048 (Ovary—dermoid)	1
Avian—9195 (testicle—tridermic), 11866 (ovary—didermic)	2
TOTAL	3

(2) *Teratoid or embryonal tumours—" False " mixed tumours.*

(*a*) Kidney—(embryonal nephroma—" adenosarcoma ").

Equine—3446, 5576	2
Bovine—3310 (1), 5648, 6455, 5207, 7093	5
Ovine—3055, 3241	2
Avian—8405, 10682, 12143, 12628, 14189 (2), 15360, 16143	7
TOTAL	16

(*b*) Mammary gland (embryonal).

Canine—6660 (=8516 =8549) (" chondrocystadenocarcinoma "), 13676 (" adenosarcoma "), 14605 (=15827) (" chondroadenosarcoma ") 15458 (" chondroadenosarcoma "), 15758 (" chondroadenosarcoma ")	6

(*c*) Other organs.

Bovine—See adrenal (malignant hypernephroma).	
Ovine—5382 (lung—" leiomyo-lympho-adenoma.")	1
Canine—7808 (1) (embryonal epulis: " carcinosarcoma ")	1
TOTAL	2

(*d*) Site unknown.

Canine—2059 (embryonal tumour: " carcinosarcoma ")	1

(3) *Collision Tumours.*

Caprine—6377 (perineum: collision of acanthoma and pigmented epithelioma)	1
Avian—15100 (ovary (3): collision of histiocytic sarcoma and myelocytoma), 10918 (4) site unknown (ditto)	2
TOTAL	3

(4) *True Mixed Tumours.*

Ovine—8187 (fibrolipoma)	1
Canine—14715 (myolipoma)	1
TOTAL	2

(5) *Papilloma and " Sarcoid "—mixed tumours of the skin (and mucosae).*

Equine—" Sarcoid " structure except where stated: 1695 (donkey), 2091 (donkey), 2275, 2601, 3309 (donkey), 4040 (mule), 4692 (=4835=5066 =6263), 6179, 6289 (mule), 6363 (sarcomatous tendency? intranuclear inclusions present), 6506 (=6740), 6813, 6973 (=7012—papilloma, with early acanthomatous tendency?), 7039 (donkey), 7727, 7838 (granulomatous type), 8093, 8117 (fibromatoid type of papilloma), 8461 (sarcoid type of papilloma), 8986, 9340, 9655, 10056 (myxomatoid type), 10972, 11303 (keloid type), 11562, 12088, 12324, 12325 (fibromatoid type), 12584, 12629, 12650 (granulomatous type), 12891, 14115 (fibromatoid type), 14841 (mule), 15103, 15172 (mule), 15266, 15405, 15792 (fibromatoid type), 15899 (fibromatoid type), 16077, 16220	43

NOTE.—All are situated on the skin or at natural orifices (sheath, eyelid, etc.).

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(1) With pulmonary metastases.
(2) Pulmonary metastases only submitted.
(3) With transcoelomic implantations of both moieties.
(4) Transcoelomic implantations of only the myelocytomatous moiety were submitted.

Bovine—Typical papillomata except where stated.	
Affecting skin or natural orifices: 3104 (sarcoid tendency), 4112, 4938, 5564, 5728, 7840 (sarcoid tendency), 8922 (sarcoid tendency), 10952 (sarcoid tendency), 11877 (sarcoid tendency), 14047 (sarcoid tendency), 14248, 14836 (=14893) (papillomatous and sarcoid types)............	12
Affecting the forestomachs (omasum): 7400, 7456; (rumen) 8210....	3
Caprine—7000 (skin, supraorbital region, papilloma)......................	1
Porcine—7943 (glottis, multiple papillomata)............................	1
Canine—(buccal papillomatosis): 14170, 14201, 14665 (osteoid papillomata)..	3
TOTAL.........................	63

Some Hyperplastic Lesions approaching Neoplastic Grade or likely to be mistaken for neoplasms.(1)

Equine—9276 (pituitary: cystic degeneration), 9990 (stomach: localised chronic inflammatory adenomatoid hyperplasia), 13077 and 13180 (thyroid: nodular hyperplasia).

Bovine—5316 and 5630 (liver: congenital bile-duct cysts), 6472 (liver: localised hyperplasia of connective tissue and smooth muscle associated with a parasitic nodule), 7919 (liver: diffuse adenomatoid hyperplasia of the bile-ducts associated with cirrhosis).

Ovine—4432 and 10471 (duodenum: adenomatoid hyperplasia of Brunner's glands).

Caprine—9647 (=9447) (thyroid: nodular hyperplasia).

Canine—9379 (mammary gland: chronic "glandular" mastitis with cystic papilliform epithelial proliferation), 9518 (lymph-node: hyperplastic lymphadenitis), 12117 (skin: localised productive dermatitis characterised by hyperkeratosis and sebaceous gland hypertrophy; cf. 10223), 15049 (liver: multiple adenomatoid hyperplasia; skin: multiple hair-follicle sebaceous gland hyperplasia; peritoneum: multiple new formation of haemal nodes).

Fowl—9319 and other cases (bowel serosa and mesentery: multiple cystic lymphangiectasia), 10638 and other cases (peritoneum: chronic productive peritonitis associated with ruptured ova, etc.), 11869 (oviducal ligament?: organisation and osteoplasia in a venous varicosity).

(1) Non-neoplastic nodules of adrenal cortical tissue, many of which could not be described as hyperplastic, and of which there are a number of examples in the collection, have not been included here.

INDEX.

NOTE.—The index of subjects and authors is combined. Joint authors are listed under the name of the senior author only. The index does not cover the information contained in the general summary, the bibliography, and the three appendices, the contents of which are already arranged for ease of reference.

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Sex Physiology of Sheep.*

By LUCIEN L. ROUX, Section of Surgery, Radiology, and Gynaecology, Onderstepoort.

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INTRODUCTION.

THE incidence of infertility among domestic animals has been the greatest stimulus towards researches upon the pathology of the genitalia of these animals (Quinlan, 1929, 1935). However, it has been realised for many years that factors also of a non-pathogenic nature are responsible for many irregularities which occur in connection with the functions of the sex organs of farm animals (Heape, 1899, 1901; Marshall, 1903; Hammond, 1914, 1921; Marshall and Hammond, 1926).

Detailed studies of sex physiology are elucidating problems which, if solved, would assist farmers in regulating the management and feeding of their stock so as to obtain maximum production during the full length of the normal life of their animals. Any degree of infertility means economic loss; moreover, the presence of inherent low fertility is transmitted to subsequent generations (Crew, 1925).

Great similarity exists between the sex organs of the main species of farm livestock (Kupfer, 1928), so that sex physiology studies of the one may very materially assist the researches on the other. Yet, in spite of the closest identity in structure of the genital organs, striking differences in function, or rhythm of function, of these organs have been found to exist, not only between closely related species, but even between breeds of the same species and this appears to be the case particularly in sheep (Heape, 1899, 1901; Marshall, 1903; Marshall and Hammond, 1926).

Pathological conditions of the genitalia of sheep are relatively seldom encountered (Marshall and Hammond, 1926), so that, in this species, the search for essential knowledge of the nature of the aetiology of infertility should concentrate largely upon genital physiology.

Such differences in sheep as the age of puberty, duration of the annual sexual season, fecundity, fertility, etc., must, to some extent, be attributed to breed characteristics. Hence, Border Leicesters, Leicesters, Dorsets, and Suffolks are among the most fertile breeds, while the Blackface is considerably less fertile due to the high incidence of barrenness (Nichols, 1924, 1926). Dorsets have two sexual seasons while other British breeds have only one annual sexual season (Roberts, 1921; Marshall, 1922). Although the fecundity of Merinos is considerably less than that of the British breeds of sheep, the sexual activity of the former breed is exceptional in that Merinos in certain parts of Australia and South Africa experience a continuous series of dioestrous cycles throughout the year, when conditions are favourable (Marshall, 1922; Quinlan and Maré, 1931).

There is, however, considerable variation in the expression of these physiological characteristics and the contention that environment plays an important rôle is not without foundation. It is of scientific interest and immense practical value to know in what way the various environic factors influence the activity of the reproductive processes, as such knowledge may bring about the introduction of methods of treatment and management which would result in greater fertility and, consequently, larger economic gains.

Climate is the principal factor in the limitation of the world's sheep population; the dense centres of sheep population are found within comparatively narrow limits of temperature, rainfall, and humidity, to which sheep are particularly sensitive during the breeding and lambing seasons (Johnson, 1924). Types of seasons have considerable influence upon the growth of sheep more especially during their first year (Hammond, 1921). Due largely to climatic preference, the heavily woolled breeds of sheep, such as the Merino, are not found to thrive in regions of high rainfall and humidity, but they prosper in the semi-arid areas in spite of wide ranges of temperatures. During poor rainfall seasons in the latter areas, Merino sheep have been said to be less fertile than during normal seasons (Quinlan and Maré, 1931).

The various types of soils and subsoils have been claimed to influence the fertility of certain British breeds of sheep. Thus, a relatively high percentage of infertility is found among Lincoln sheep run on the wolds, Shropshires on a subsoil of New Red Sandstone, and Hampshires which are not run on chalk downs (Heape, 1899). In South Africa, the insufficiency of phosphorus in the soil has been shown to be the cause of infertility in cattle (du Toit and Bisschop, 1929) and evidence exists that the reproductive powers of sheep are affected in a similar manner (Bekker, 1932).

The type, abundance, and nutritive value of natural pastures are the principal factors which determine the sheep-carrying capacity and the success of sheep farming in any area. Malnutrition, due to deficiencies in pastures, most commonly occurs in old countries on uncultivated grazings to which no return has been made to compensate for the value taken from them, or in new countries where the native stock has been improved without a corresponding grading up of the pastures. Such deficiencies generally result in emaciation; in young animals growth is stunted, while in mature animals the breeding capacity is affected (Orr, 1929). This problem of deficiencies in pastures is of particular interest in South Africa, where the natural grazing in large tracts of otherwise good sheep country becomes so leached of nutritive value during the winter months, that sheep are unable to continue the normal processes of production and reproduction unless supplementary feed is supplied.

With adequate feed and in the absence of disease, normal growth and development of the animal body take place. During the early stages of life, the sex organs develop at an equivalent rate to that of the rest of the body, and the age of puberty marks the commencement of the cyclical changes in the female, which cease only when old age overcomes general ability and the sex organs undergo gradual atrophy (Robson, 1934). While no definite data exist to indicate the normal sexual life in sheep, what is maintained in the case of cattle no doubt can be applied to sheep, namely that considerable variations due to breed and feed exist (Hammond, 1927) The same changes which initiate the activity of the sex organs of the female at puberty, bring about the cyclical secretory and morphological effects at periods when the behaviour of the animal indicates the occurrence of oestrus. The morphological changes which take place in the uterus, fallopian tubes, and vagina, are under control of specific substances (hormones) which are produced by the ovaries. Furthermore, the activities of the ovaries are under the control of hormonic substances secreted by the anterior pituitary gland, but the factors which determine the activity of the anterior pituitary lobe have not been identified (Robson, 1934).

It must be apparent from the above remarks that: (1) In spite of similarity of the associated organs and the principles governing physiological phenomena in various breeds of sheep, certain differences are fundamentally specific and breed characteristics and such differences are reflected largely in degrees of fertility.

(2) Environic factors are responsible for a certain amount of diversity of intensity of the activity of the reproductive organs. Adverse conditions such as scarcity of feed or malnutrition result in inactivity of the reproductive organs which is reflected in infertility.

The Merino sheep population of South Africa is approximately 40 millions, the non-woolled breeds constitute about 5 millions, while the improved mutton (British) breeds exist in very small numbers. The Merino sheep industry is, therefore, of immense importance to South Africa.

It has been stated that the fertility of Merino sheep in South Africa is decidedly lower than that of sheep in Europe (Nichols, 1926); Quinlan and Maré (1931) obtained 77·7 per cent. fertility in Merinos and they state that, under less favourable conditions on South African farms, fertility is infinitely lower. It is, therefore, evident that great importance must be attached to information upon the physiology of breeding and especially to all problems affecting fertility of Merino sheep in South Africa.

The physiological changes in the ovaries of Merino sheep in South Africa, and their practical application in breeding have been studied in great detail (Quinlan and Maré, 1931). However, it is interesting to note that certain of these observations do not entirely agree with those made by Küpfer (1928), under different conditions in the same country. The varying results obtained by Küpfer were considered by Quinlan and Maré likely to be due to abnormal adverse seasonal conditions.

In certain observations made by the author, preliminary to those reported in this thesis, there appeared to be a certain similarity to the results recorded by Küpfer (1928) under western Free State conditions, rather than to that of Quinlan and Maré (1931), whose observations were made under Cape Karroo conditions. The main feature of the difference was the duration of the sexual season. According to Quinlan and Maré, Merino sheep in South Africa experience a continuous series of dioestrous cycles throughout the year, whereas Küpfer observed the existence of a prolonged anoestrous period in non-pregnant Merino ewes, during which period ovarian activity is in abeyance. It appears important to establish whether environic factors constitute the main cause for such differences in ovarian activity, and whether deviations in the cyclical activities of the ovaries can be brought about by subjecting sheep to various treatments for extended periods of time.

REVIEW OF THE LITERATURE.

THE SEXUAL SEASON.

The sexual season is the period of the year during which the non-pregnant ewe exhibits oestrus or a series of dioestrous cycles (Heape, 1900).

Sufficient information has been accumulated to establish the fact that, in most types and breeds of sheep in many countries, the sexual season is restricted to a particular time of the year, namely the autumn and early winter months (Heape, 1900; Marshall, 1903, 1922; Küpfer, 1928; Cole and Miller, 1933; Grant, 1934). From Marshall's (1922) accumulation of the earlier information, it is evident that the wild types of sheep are monoestrous, but that the domestic breeds are polyoestrous in that they experience a series of dioestrous cycles during the sexual season. The latter information has been confirmed by the more recent authors in whose observations the British and Merino breeds of sheep were included.

Instances have been reported which reveal that, in certain limited cases, sexual activity of the non-pregnant ewe is exhibited annually in two sexual seasons (Wallace, 1896; Roberts, 1921; Marshall, 1922; Marshall and Hammond, 1925). This peculiarity appears to occur particularly in Dorset Horn and Merino sheep.

Furthermore, there is evidence to indicate that Merino sheep in certain parts of Australia and South Africa and certain breeds in Central Europe are found to experience non-restricted sexual activity, or a continuous series of dioestrous cycles, throughout the year (Marshall, 1922; Küpfer, 1928; Quinlan and Maré, 1931).

It may be said, therefore, that there appears to be a gradual increase of sexual activity from the monoestrous condition of the wild species to the extreme degree of polyoestrum exhibited by certain domestic breeds of sheep.

THE ANOESTROUS PERIOD OR ANOESTRUM.

The anoestrous period is the period of rest during which there is complete sexual quiescence; anoestrum occurs between the sexual seasons (Heape, 1900).

From the information cited on the sexual season, it becomes obvious that the duration of the anoestrous period decreases from that of the monoestrous wild types to that of the polyoestrous domestic breeds of sheep.

The British breeds of sheep, in their home country and abroad, experience an anoestrous period and, although some variation exists as to the length of anoestrum, the latter occurs during the spring and summer months (Heape, 1900; Marshall, 1903, 1922; Marshall and Hammond, 1926; Roberts, 1921; Cole and Miller, 1933; Grant, 1934).

Küpfer (1928) reports that the sheep of Central Europe have no annual anoestrum and, according to Marshall (1922) and Quinlan and Maré (1931), Merino sheep in certain parts ot Australia and South Africa do not experience an annual anoestrum. However, Küpfer's (1928) observations on Merino and Woolled-Persian sheep in South Africa definitely indicate the existence of a prolonged anoestrous period. It is interesting to note that Küpfer found the same condition of anoestrum to exist in Boer and Angora goats during the spring and summer months under South African conditions and the observations of Warwick and co-workers (1933) on Angora goats in Texas agree with those of Küupfer on the same species; the former authors report an anoestrous period during the Texas spring and summer months.

Various reasons are advanced to explain the differences in annual sexual activity of the types and breeds of sheep. A certain amount of importance is attached to genetic differences, while at the same time it is realised that such factors as feed and climate may modify the degree of sexual activity of the non-pregnant ewe. The available information relating to these aspects of the sexual season and anoestrum is given under a subsequent section of this review.

The Dioestrous Cycle.

It has been indicated that the sexual season of the non-pregnant ewe is made up of a series of dioestrous cycles. Each dioestrous cycle consists of: prooestrum, oestrus, metoestrum, and dioestrum, (Heape, 1900).

Prooestrum.

In sheep, the external signs of prooestrum are slight, although they have been detected as being a congestion of the vulva and a discharge of mucus (Marshall, 1922; Grant, 1934).

Quinlan and Maré (1931) observed that in Merino sheep oestrus comes on gradually over a period of several hours, but Grant (1934) found that in Scottish sheep receptivity is reached within 30 to 60 minutes.

Oestrus.

" Oestrus is the special period of desire in the female; it is during oestrus, and only at that time, that the female is willing to receive the male and fruitful coition rendered possible " (Heape 1900).

The external symptoms of oestrus in the ewe have been described by Marshall (1903), McKenzie and Phillips (1930), and Grant (1934). The mutual behaviour of the ewe and ram is a reliable indication of oestrus. A non-receptive ewe runs away when approached by the ram, while a receptive ewe goes in search of or goes to meet the ram; attention from the ram causes the ewe to vibrate her tail and she allows the ram to mount or to serve her. The external signs of prooestrum persist during oestrus.

Considerable variation in the duration of oestrus has been observed. Heape (1900) considers that in Barbary wild sheep oestrus lasts only a few hours, while in domestic sheep it lasts probably 12 hours. McKenzie and Phillips (1930) in a study of 247 periods found an average duration of 26·8 hours in Hampshire, Southdown, and Shropshire sheep; the shortest and longest periods were 5 and 50 hours respectively and seventy-four per cent. of the periods were 18 to 36 hours. Significant differences were found to exist between the duration of oestrus of the different breeds and significant differences were found between lambs and yearlings; however, such differences were not revealed between yearlings and older ewes. Grant (1934) observed that in Scottish sheep the duration of oestrus ranged between 3 and 84 hours, the mean was 22 hours and the mode 28 hours. McKenzie and Phillips and Grant observed the duration of oestrus by means of " keeled " vasectomised and vasoligated rams, frequent inspections for marked ewes having been made. Quinlan and Maré (1931) tested Merino ewes at twelve-hour intervals and they found the average duration of oestrus to be 40 hours, the mode 36 hours, and the range 24 to 96 hours.

Metoestrum.

Metoestrum, the waning of oestrus, is gradual; it lasts for a period of several hours (Quinlan and Maré, 1931; Grant, 1934).

Dioestrum.

Dioestrum is the period of the dioestrous cycle during which no sexual desire is shown; it is an interval of quiescence (Heape, 1900; Marshall, 1922). Heape considers that the two quiescent periods, dioestrum and anoestrum, are homologous, that the one is a modification of the other, and that " the modification is no doubt related to an increased or decreased power of reproduction ".

Quinlan and Maré (1931) found the length of dioestrum in Merinos to range from 12·5 to 17 days and the mode is given as 15 days.

Periodicity of Oestrus.

Usually, oestrus recurs with marked regularity during the sexual season. The periodicity of oestrus, or the length of the dioestrous cycle, depends largely upon the duration of oestrus and dioestrum.

Quinlan and Maré (1931), and Quinlan, Maré, and Roux (1930), (1932) found the mode of the dioestrous cycle in Merinos to be 17 days and, while the great majority of cycles were 16 to 18 days, cycles as short as 6 days and as long as 68 were observed. McKenzie and Phillips (1930) report an average dioestrous cycle of 16·6 days for certain British breeds of sheep; 79 per cent. had cycles from 14 to 16 days; there were no significant differences due to age and breed. Grant (1934) found the mean duration of the dioestrous cycle in Scottish sheep to be 16·4 days, the mean deviation being ±0·8 days. He points out that Küpfer (1928), Sanctis (1926), and Schmaltz (1921), found a somewhat longer cycle to exist in Central European sheep and, by compiling all available data, Grant gives the average duration of the cycle as 16·8 days and the mode as 17 days.

Variations in the length of successive dioestrous cycles are small. Quinlan, Maré, and Roux (1932) found that in 45 per cent. of cases no variation occurred while variations of one day occurred in 45 per cent. of cases.

Considerable evidence is available to indicate that the interval between two exhibitions of oestrus is frequently the length of two or even more dioestrous cycles. Grant (1934) suspects that in cases in which observations are made only once daily, short oestrous periods might be missed, but he points out that, even when " keeled " rams were run with the ewes constantly, abnormally long interoestrous periods were observed by McKenzie and Phillips (1930) and Casida and McKenzie (1932).

THE CHANGES IN THE REPRODUCTIVE ORGANS.

The preceding details deal with the external manifestations of sexual activity in the non-pregnant ewe. It is now necessary to consider briefly the rhythmic alterations occurring in the reproductive organs and to indicate the relationship between the various sex organs.

It is not necessary to enter into great detail upon the anatomical structure and the physiological changes experienced by the genital organs. Such details can be found in the well-known text-books and monographs on reproduction in mammals. However, for the present purpose, the periodic changes experienced by the ovaries appear to warrant special attention.

The morphological and physiological changes occurring in the reproductive organs of the non-pregnant ewe have been studied by Marshall (1903), Küpfer (1928), Quinlan and Maré (1931), Casida and McKenzie (1933), and Grant (1934).

The researches of certain of the above investigators (Marshall, Küpfer, Casida and McKenzie, and Grant) indicate that during anoestrum all the sex organs are in a quiescent and anaemic state; the ovaries are small and compact, but many small follicles may be present. Grant states that it is not known whether the follicles are constantly growing and regressing during anoestrum or whether follicular development is entirely arrested. About six weeks prior to the commencement of the sexual season, mitosis begins in the reproductive organs and eventually the latter assume the condition evidenced during the oestrous period. Grant's findings reveal that one or more cycles of ovulation and development of corpora lutea may occur before the regular sexual season, while occasionally an ovarian cycle takes place without the exhibition of heat at the end of the sexual season. Küpfer (1928) also observed the occurrence of ovulation without oestrus and he is of the opinion that such ovulations would not lead to pregnancy.

During the dioestrous cycles of the sexual season, many alterations take place in the ovaries, uterus, and other secondary sex organs (vagina, cervix, fallopian tubes). During the interoestrous period, or dioestrum, the organs prepare for the reproductive climax, oestrus, when the uterus is enlarged and distended and ovulation takes place.

The morphological changes in the ovaries during a dioestrous cycle embrace: follicular maturation, ovulation, and the formation and subsequent atrophy of luteal tissue. The secretory changes in the ovaries result in the liberation of a specific hormonic substance, oestrin, which, together with the corpus luteum hormone, controls the cyclical alterations in the various divisions of the uterus.

Through ovarian control, the endometrium or internal and secretory grandular portion of the uterus undergoes changes necessary for the nidation of the ovum. During the latter part of oestrus, the fallopian tubes and uterus are in a fit state for the reception of the ovum.

More recently, it has been discovered that both the morphological and secretory changes in the ovaries are subject to a specific hormonic control by the anterior lobe of the pituitary (Zondek and Aschheim, 1927; Smith and Engle, 1927—*cit.* Robson, 1934). Hence, the influence of the substances capable of being excreted by the pituitary upon the ovaries may bring about: (*a*) follicular maturation, ovulation, and oestrin secretion, and (*b*) the formation of luteal tissue, followed by the secretion of luteal hormone which results in the inhibition of oestrus.

The Specific Changes in the Ovary.

As the changes in the ovaries are of particular interest in the present sudy, it appears necessary to review the literature upon the ovarian activity of the ewe in considerable detail.

From a practical point of view, early conception, regularity of lambing, and the number of lambs born out of a single ewe or a flock of ewes, are indications of ovarian activity. Hammond (1921) points out that the number of ova shed is the main factor influencing fertility, but the same author draws attention to the fact that foetal atrophy and unobserved early abortions do occur in sheep. Clark (1934) found that ovulation rates are approximately the same as the lambing averages. However, the probability of the presence of rams of varying fertility must not be lost sight of in cases in which the fertility of the ewe is used as a measure of ovarian activity (Quinlan and Maré, 1931; McKenzie and Phillips, 1933). Nichols (1924, 1926) draws attention to various environic factors which may affect fertility. Therefore, a true reflection of ovarian activity is not obtained by considering lambing percentages and this may be the case especially when marked low fertility is observed. However, the possibility of the above irregularities existing does not condemn a restricted use of data on lambing percentages, more especially when the animals considered have been maintained under similar conditions and management, and the number of animals considered is large. Lambing results are, therefore, referred to in this and subsequent sections of this review. On the other hand, it must be emphasised that greater importance is attached to oestrous observations and even more to the examination of the ovaries as being reliable methods of determining and studying ovarian activity.

Puberty marks the onset of ovarian changes. Marshall (1922) remarks that puberty is not accomplished at once. It is the period during which the animal becomes sexually mature when the essential organs of reproduction undergo a great increase in size.

Evidence exists which indicates that, even at a very young stage, the ovaries are not entirely static: Hammond (1927) cites the reports of Heitz (1906) and Käppeli (1908) stating that out of 75 ovaries of calves between 5 and 12 weeks old, 80 per cent. contained a follicle over 0·3 c.m. in diameter, and that in four cases a folicle of 1·3 c.m. was found. Robson (1934) contends that it is generally accepted that in mammals a large number of ova are present in the ovaries at birth, but that they remain quiescent until maturity.

Marshall and Hammond (1925) consider that during growth the internal secretions are concerned with growth and that the secretions are insufficient for the development of sex cells. Parkes (1929) points out that the idea of somatic control of the ovaries has been vindicated by recent work on the effects of the anterior pituitary substance on the ovaries. The same author says that the development of the ovaries before puberty tends to be sporadic; it may include one or more waves of growth which are followed by retrogressive changes.

Although little exact information with regard to the age of puberty of sheep is available, evidence indicates that ewes of 9 to 12 months are sexually mature; yet considerable variation between breeds and individuals within breeds appears to exist. McKenzie and Phillips (1930) found that the age of puberty in Hampshire, Shropshire, and Southdown sheep varies considerably, the first named breed being well in advance of the others. Well grown Hampshire lambs averaging 86 pounds exhibited their first oestrus when from 187 to 250 days old. According to Quinlan, Maré, and Roux (1930), 50 Merino ewes under oestrous observation showed oestrus at 9 to 10 months old; but, according to an analysis of other data presented by the same authors, 11·4 per cent. of the 50 Merino ewes when 18 months old, did not show oestrus during four consecutive months of observation and under conditions where Merinos are maintained to be sexually active throughout the year. Griswold (1932) found that Hampshire-Rambouillet ewes bred as lambs gave an 86 per cent. lamb crop. Golf (1934) reported 129 per cent. lambs in German Mutton Merino sheep bred at 10 to 12 months of age. Nichols (1926) points out that barrenness in shearing (young) ewes is due frequently to failure to take the ram which may be due to sexual immaturity, hence reduced or delayed ovulation.

Robson (1934) in reviewing the work of Smith and Dortzbach (1929) and Wolfe and Cleveland (1931) on the secretions of the anterior pituitary of immature animals, states that " . . . . the anterior pituitary lobe contains active gonadtrophic hormones before the onset of maturity and the ovary is capable of reacting to these hormones and yet under normal physiological conditions the ovary does not mature at that time. Up to the present no satisfactory explanation for this apparent paradox has been found ". Robson considers that, as the injection of additional hormone into immature animals brings about sexual activity, it is likely that the rate of secretion of the untreated immature animals is not at a sufficiently high level to stimulate the ovary.

Descriptions of the ovary of mature ewes have been given by many writers and more recently by Küpfer (1928), Quinlan and Maré (1931), and Grant (1934).

The number of follicles which rupture during any one oestrus varies. Grant found that out of a total of 441 ewes, the average number of corpora lutea present was 1·87; there were 54 ewes with 3 corpora, 8 with 4, and 3 with 5 corpora. The average number of corpora found present by Marshall (1903) was 1·25 and by Hammond (1921) 1·45. It appears from the work of Quinlan and Maré (1931)on Merino sheep, that the liberation of more than one ovum seldom occurs. Grant (1934) states that there is a tendency for the number of ova shed to decrease towards the end of the sexual season. On the other hand, Clark (1934) states that cases of double ovulation occur fairly uniformly throughout the sexual season.

Usually, follicles of various sizes are found in the ovaries, but all these follicles do not mature as, after ovulation, the remaining follicles degenerate (Sandes, 1903—*cit.* Hammond, 1914). Marshall (1922) considers follicular atrophy a natural process; only when it becomes excessive does it result in sterility, in which case the failure of some follicles to mature is probably due to insufficiency of stimulating power at the disposal of the ewe.

According to Quinlan and Maré (1931), shortly after ovulation there is rapid enlargement of the follicle destined to rupture at the next oestrus, but Grant (1934) found little early development, growth taking place uniformly throughout the interoestrous period. In the sow, McKenzie (1926) found the growth of follicles to be slow during the early part of the interoestrous period, but very rapid about three days before the onset of oestrus.

The final stages of the mature follicle in the ovary of the ewe have been described by Küpfer (1928), Quinlan and Maré (1931), and Grant (1934). At the commencement of oestrus, well developed follicles reach a diameter of about 1 c.m., the capsule is thin and transparent, the contents appear slightly purple in colour, and one or two capillaries are seen transversing the follicular capsule. Rupture of the follicle is preceded by the elevation of a small papilla above the general surface and ultimately the immediate cause of the rupture is considered to be the pressure of the follicular fluid. While one ovulation from each ovary may occur, a double ovulation from one ovary has been evidenced; also, the same ovary may ovulate three times in succession.

Grant (1934) indicates the variations reported with regard to the time of ovulation relative to the onset of oestrus. It appears that in most cases ovulation occurs 24 hours subsequent to the onset of oestrus. In Merinos, Quinlan and Maré (1931) state that ovulation rarely takes place before the 36th to the 40th hour of oestrus. Grant considers that it occurs earlier in Scottish sheep than in other breeds. Green and Winters (1935) state that ovulation in sheep occurs as the animal passes from heat.

Normally, ovulation does not occur during pregnancy, during which period the follicles remain small and unaltered (Quinlan and Maré, 1931). However, authentic cases of superfoetation have been reported by Smith (1927, *cit.* Grant, 1934) and Grant (1934).

Ovulation has been observed 10 to 15 days post-partum, but such ovulations are not accompanied as a rule by oestrus when the ewe suckles its lamb (Quinlan and Maré, 1931). Parkes (1929) indicates that it has been shown by practising ovarectomy that the inhibition of oestrus during lactation is set up through the ovary, and that the absence of oestrus is not due to the heavy drain upon metabolism resulting from lactation.

Oestrus has been observed to occur soon after abortion. Nichols (1924) reported a case in which a ewe aborted during early pregnancy and was served the following day. Quinlan and Maré (1931) observed normal oestrus in a Merino ewe 17 days after the birth of a still-born lamb and, in a similar type of case, van Rensburg (1935) observed normal oestrus after 21 days.

Shortly after ovulation, luteal cells are formed by " the hypertrophy of the follicular epithelial cells and the ingrowth of connective tissue along with blood vessels " (Robson, 1934). The evolutionary and involutionary changes of the corpus luteum in the ovary of the ewe have beeen described by Küpfer (1928), Quinlan and Maré (1931), Casida and McKenzie (1933), and Grant (1934). The corpus luteum becomes conspicuous 48 hours after ovulation; within five days it occupies a large portion of the ovary, when it may be 0·5-0·7 c.m. in diameter; it reaches its maximum size at about the middle of the interovulation period of its formation, when it is about 0·9 c.m. large and has a central cavity containing a fluid. As its cycle advances, it changes from a blood red to an opaque pink colour. Although Quinlan and Maré state that the corpus luteum remains little changed in size until after the commencement of the next oestrus, the other investigators report that the corpus starts degenerating during the latter part of the interovulation period. Atrophy becomes rapid after the formation of the newly formed corpus luteum and the colour changes to a yellow, then to a dark brownish yellow. The last trace of the corpus is a brownish pin-point speck on the surface of the ovary. Grant's (1934) statement to the effect that Quinlan and Maré (1931) misinterpreted the changes in the corpus luteum prior to ovulation, does not appear to be substantiated. The ovaries shown in the coloured drawing submitted by the latter authors, are of natural size and they were made from the fresh ovaries taken from sheep immediately after slaughter. Moreover, it is very evident that the greatest care was taken in representing the appearance of the corpus luteum from day to day during the inter-oestrous period.

The corpus luteum of oestrus is a ductless gland and its chief function is the inhibition of oestrus, which effect it produces by a specific hormone.

The corpus luteum of pregnancy, or corpus luteum vera, is highly vascular and it remains present in the ovary during the entire period of pregnancy (Quinlan and Maré, 1931). However, by the end of the third month slight changes commence, but more marked alterations in size and colour are noticed just previous to parturition, after which rapid changes in size take place.

During lactation, atrophy of the corpus luteum vera continues, and three months after parturition, it is reduced to a vestige (Grant, 1934). Only in rare cases does ovulation occur shortly after parturition (Quinlan and Maré, 1931). In spite of the absence of a corpus luteum, oestrus does not generally occur during lactation; Hammond (1925, *cit.* Robson, 1934) has suggested that lactation interferes with the nutrition of the ovaries thus inhibiting the occurrence of normal dioestrous cycles.

As previously indicated, the corpus luteum is a gland of internal secretion and the hormone which it secretes assists the ovarian hormone, oestrin, in regulating the cyclical alterations in the various divisions of the uterus. Although it is generally understood that secretions of the corpus luteum inhibit oestrus, Robson (1934) states: "None of the evidence so far adduced, however, proves conclusively that the inhibitary effect upon oestrus is definitely due to known luteal hormones and the possibility that unknown or even an unspecific factor may be responsible for some of the results observed has by no means been excluded. Moreover, it is known that other substances besides the luteal extracts have an inhibitary action on the occurrence of oestrus, e.g. adrenaline" (Robson, 1932). Robson in his review also indicates that it appears to be definitely established that the luteal hormone is important in the early stages of gestation in all species, but that the contentions with regard to the function of the corpus luteum during subsequent stages of gestation are contradictory. It is not definitely known whether there is any interrelation between the corpus luteum and the mammary gland.

Aschheim and Zondek (1927) and Smith (1927, *cit.* Robson, 1934) discovered that large quantities of oestrin are excreted in pregnancy urine. Zondek (1930—*cit.* Robson, 1934) has standardised two gonadotropic substances, Prolan A. and B., recoverable from pregnancy urine or from the pituitary, in terms of mouse or rat units. While a considerable measure of success has been achieved by artificially inducing ovulation and oestrus in small animals through the administration of preparations containing gonad stimulating hormones, only in limited instances have similar successes been achieved with domestic animals such as the ewe. Cole and Miller (1933) found that oestrus and ovulation can be induced in sheep during mid-anoestrum by administering sufficient amounts of gonad stimulating hormones in serum from pregnant mares. The importance of giving a second injection of the serum 16 days after the first is stressed. Warwick and co-workers (1933) used a serum prepared from human pregnancy urine on goats and, while ovulation was found to have occurred in several cases, oestrus was not produced. As details were not given in the report available, it is not known whether the precaution of giving the second injection after a particular time was observed.

THE GENETIC ASPECTS OF OVARIAN ACTIVITY.

During the consideration of the sexual season in the various breeds and types of sheep, it was deduced that there appeared to be a gradual increase of sexual activity from the monoestrous condition of the wild species to the extreme degree of polyoestrum exhibited by certain domestic breeds of sheep.

Marshall's (1922) accumulated information on the wild types of sheep, O. tragelophus, O. burrhel, O. musiman, O. vignei, O. ammon, O. canadensis, O. poli, and O. argili, indicates that they are all monoestrous. Parkes (1929) states that the wild prototypes of the cow, pig, sheep, and goat, all probably exhibit a restricted sexual season, which in the case of the last two appears to be in the autumn, but that domestication extended the season so that domestic strains breed at almost any time. He further states that, in the domestic strains, the greatest readiness to breed it still found at the time which corresponds to the primitive sexual season.

Through domestication, improved methods of husbandry no doubt have encouraged the establishment of longer sexual seasons, which increased the probability of fertilisation and consequently the fertility of the flocks. Marshall (1903, 1922) and Marshall and Hammond (1925) indicate that variations in the time of the occurrence and the duration of the sexual season are definitely breed or racial characteristics. While most breeds in Great Britain experience many dioestrous cycles during their annual sexual season, the Scottish Blackfaced sheep in the Highlands have only two dioestrous cycles annually. While the sexual season of most British breeds of sheep is from October to February, the Limestone sheep of Westmorland and Derbyshire and Dorset Horn sheep are capable of breeding more than once annually. Roberts (1921) found that, in the United States, Shropshires are most active during October to December, while in Dorsets two annual sexual seasons occur during the months May to July and September to December. As previously indicated, Merino sheep in certain parts of Australia and South Africa experience greater annual sexual activity than any other breed, as in the former a continuous series of dioestrous cycles is experienced throughout the year (Marshall, 1922; Quinlan and Maré, 1931).

In comparing the early breeding characteristics of various breeds, Darlow (no date) and Russell (1919) found significant differences. The Merino was the best early lamb producer; 80 per cent. of the ewes brought lambs before January as compared with 40 per cent. of the Dorsets. Although the Shropshire was found to be a late breeder, the Shropshire-Merino crosses were earlier breeders than the Merino. Darlow states that, while the early breeding character is not common to all Dorsets, it appears to be particularly dominant over late breeding when the Dorsets are selected for the former character.

As previously indicated, fertility can, to some extent, be used as an indication of ovarian activity. Heape (1889) found remarkable differences in the fertility of various breeds and he contended that the results of his investigation clearly indicated that fertility is a racial characteristic. Heape remarked upon the remarkably high fertility of Suffolks, Shropshire, and Dorsets and the serious state of low fertility among Southdowns of those times. The later investigations of Nichols (1924, 1926) led to the definite conclusion that differences in fertility between different breeds and within breeds are fundamentally genetic. Marshall and Potts (1924) state that various breeds and strains have each an inherited limit of fertility. In comparing the fertility of several breeds of sheep in the United States, they found that Dorsets gave the best returns and Rambouillets lowest returns per 100 ewes; whereas 146 and 163 per cent. were obtained from two year old and aged Dorset ewes respectively, the equivalent returns from Rambouillets were 111 and 125 per cent.

It is logical that the factors which yield high fertility are those which produce a high proportion of multi-births. Hammond (1921) has indicated that the limiting factor in fecundity is the number of ova shed at oestrus. Age appears to play an important role so far as fecundity and, consequently, ovarian activity are concerned; although variation between different breeds exists, greatest fecundity occurs during the sixth year of the ewe's life. Marshall and Potts (1924) have shown that analyses of flock records indicate an increase in proportion of twins born until ewes are 5 to 6 years old; ewes 2 years old produced 111·4 per cent. lambs, while 6 year old ewes yielded 161·2 per cent. lambs. In American Shropshire sheep, the percentage of multi-births increases up to 4 years and then remains fairly constant through the eighth year; ewes 16 years old were productive (Roberts, 1921). Langlet (1934) reports that in German Mutton Merinos optimum lambing results are obtained in the sixth year, but in German white-headed mutton sheep best lambings are obtained from ewes 3 to 4 years old. As old ewes are either sold or slaughtered before they reach senility the full extent of their reproductive ability is usually unknown. However, Pearl (1913) has reported a case of abnormal fecundity in a " native " ewe which gave a farmer 19 fleeces and 36 lambs. The breeding details were as follows: first 2 years, 2 singles; third year, twins; next 6 years, triplets; next 6 years, twins; next 2 years, singles; last 2 years, no lambs.

Pearl (1912, *cit.* Hammond, 1914), has shown that a fertile strain of fowl does not necessarily contain more oocytes in its ovaries than an infertile strain and that the development and growth of the oocytes are caused by a physiological factor. Crew (1925) contends that it is possible to bring a family of animals to an end by deliberately neglecting the fact that its individuals are of low fertility. Marshall and Hammond (1925) draw attention to the importance of using rams from highly fertile strains in order to maintain or increase the fertility of flocks through their genetic constitution. Crew (1925) draws attention to the fact that, while it is possible to increase the number and intensity of the dioestrous cycles in polyoestrous animals, there is no evidence that special treatment can convert the constitutionally monoestrous into the polyoestrous, and that, although environic factors may affect the oestrous cycle, it is certain " that differences in the nature of this cycle fundamentally are specific and breed characters ".

THE EFFECT OF ENVIRONIC FACTORS UPON OVARIAN ACTIVITY.

Climatic.

Considerable evidence has been advanced to indicate that environic factors such as climate, soil, and nutrition, influence the extent of sexual activity in sheep.

Marshall (1922) is of the opinion that the occurrence of the sexual season in any one country or locality is closely connected with the climatic conditions and the periodicity of the seasons; sheep in Great Britain and South Africa adhere to this rule as in both countries they breed in the autumn. Marshall contends that the breeding season is controlled through natural selection by the needs of the next generation.

Variation in the duration of the sexual season is found to result due to changes of environmental conditions. Thus, Scotch Black-faced sheep in the Highlands experience only two dioestrous cycles during the annual sexual season, but in the Lowlands as many as five or six dioestrous cycles have been observed (Marshall, 1922). Wallace (1896) states that, in South Africa at high altitudes where sheep depend only on the veld, lambing begins in September or October. He indicates a lull in lambing due to ewes not coming in season, but he states that in the low country, below the second range of mountains, autumn lambs are obtained, which indicates that a sexual season must have occurred in the spring.

Küpfer (1928) found that under South African western Free State conditions, Merinos and Woolled Persian sheep and Boer and Angora goats are sexually active only during the autumn and early winter months. Küpfer, realising that greater sexual activity is shown by Merinos in Australia (Marshall, 1922) and sheep in Central Europe (Küpfer, 1928), considers that sheep in South Africa have adapted their ovarian functions to climatic conditions. He doubts " . . . whether sheep in various parts in any country or in different countries conform to the same type of organogenesis and follow the same periodicity in organic functions ". This author considers that the short period of sexual activity observed by him under South African conditions might be an adaptation to the conditions necessary for the rearing of the offspring. It is interesting to note that this generalization is supported by the same author's observations on equines in South Africa (Küpfer, 1928). Küpfer found that, in horses and donkeys, sexual activity was limited to the months October to March, so that, after a gestation period of about eleven months, parturition takes place at the beginning of and during the spring ,when conditions are favourable for lactation.

On the other hand, under the semi-arid conditions of the South African Karroo, Quinlan and Maré (1931) observed continuous annual sexual activity in Merino sheep. They state that, under Karroo conditions, the absence of rain for extended periods adversely affects the pasture and results in irregularity of the dioestrous cycles.

Some interesting observations upon sheep imported into the United States were recorded by Russel (1919). It was found that imported Dorset Horns were not as fertile as acclimated Dorset Horns, as, in the case of the former, 10 per cent. proved barren, 20 per cent. failed to breed before the autumn during the first two seasons, and

50 per cent. of those that lambed dropped twins. In the case of Shropshires, out of 17 ewes, 6 proved barren. Although no data are reported, Quinlan and Maré (1931) state that they consider that it takes six months for the acclimatisation in South Africa of British breeds of sheep. Also, the same authors are of the opinion that temporary sexual inactivity may result when sheep are transferred from humid coastal regions to dry Karroo conditions.

Endeavours have been made to recognise the independent effects of climate and nutrition upon sexual activity in sheep, but little information is based upon actual experimentation.

Johnson (1924), in considering the densely sheep-populated regions of the world with respect to temperature, rainfall, and humidity, states, that in the most important sheep countries of the world, the winters are mild, the summers are cool, and the humidity is considerably lower in summer than in winter. Under such conditions, the mean temperature ranges between 28° and 77° F., the rainfall between 0·3 and 4·5 inches per month, and the relative humidity between 55 and 70 per cent. at the higher temperatures and 65 to 91 per cent. at the lower temperatures. Johnson further states that the " rutting season " falls within narrow limits of temperature, rainfall, and humidiy. He appears to agree with Hammond's (1921) contention that the " rutting season " comes with a falling temperature, and it is said that, when the late summers and autumns are hot, the ewes will not breed until late. The results of Asdell's (1926) analysis of the Kid Register of the British Goat Society clearly supports his contention with regard to the relationship between temperature and sexual activity in caprines. Asdell states that it is just as the reproductive period is setting in, or as the ovary awakens from the quiescence of anoestrum, that the influence of temperature is most felt. Slight activity starts in June, the rise is gradual during July and August, after which it becomes steep, and a maximum is attained in October; there is a slight decline to November, after which the decline is steeper, and it becomes more gradual until a minimum is reached in May. This author considers the August temperature most important and, while hot summers were found to delay matings, very cold temperatures during December resulted in a smaller number of mating during that particular year. McKenzie and Phillips (1932) found that, when ewes were subjected to low temperatures (44°-48°) in an ice chamber during the day or the night for 10 days, there were no significant differences between the experimental and the control ewes in so far as the number of days required for the ewes to show oestrus was concerned. Elpatjevskii (1934) states that low temperatures below 15° C. reduced the number of sheep coming on " heat " by 25·8 per cent.; the effect of cold weather was enhanced by windy weather. Also, dull cloudy weather had a harmful influence and snow-fall reduced the number of ewes showing " heat " by 17·5 to 30·0 per cent. Asdell (1926) considers the thermo-regularity mechanism of importance, but not absolute in action, and that summer heat probably increases the temperature of most animals, especially of those in which the sweat glands are poorly developed, as for example, the sheep and goat. Asdell suggests that summer temperatures may be above that at which follicular development may be possible, winter temperatures may be below, while spring and autumn temperatures may be most suitable. He further suggests that animals with a polyoestrous breeding season which lasts practically the whole year, appear to be those in which the temperature regulatory system is most efficient.

Nutritional.

The effects of nutrition upon sexual activity of ewes have been subject to much discussion and this is especially true of the practice of " flushing ".

The advantages of " flushing " ewes some time before the commencement of the breeding season are explained and supported by Marshall (1903, 1922), and Marshall and Hammond (1925). It is advocated that ewes entering the sexual season should be in a growing or gaining condition. At the beginning of the sexual season, feed is still comparatively plentiful and the authors found that the greater percentage of twins are born during the first part of the lambing season which would indicate that the generative activity of ewes tends to be greatest at the commencement of the sexual season.

Marshall and Potts (1924) made observations on the effects of " flushing " on a total of over 350 ewes, and they found that the " flushed " ewes gave 18·7 lambs more per 100 ewes than did the " unflushed " groups. However, it is indicated that " flushing " with grain showed no advantage over good pasture grazing, nor could it be said that " flushing " brought ewes to service earlier, and it is surprising to note that more cases of returning for a second and third service were found among the " flushed " groups.

Satisfactory results from " flushing " have been reported by Okulicev (1934) who states that the practice decreased the number of barren ewes and it increased the percentage of multibirths; while the number of lambs per 100 ewes was 103 in the control group, the " flushed " groups gave 120, 112, and 110 lambs.

Nichols (1926) is of the opinion that the manner in which the " flush " is produced is not as important as the fact that there has been " flushing " or a change to good fresh pasture. Nichols considers it imperative to practice " flushing " every year, for, if this is not done, lambing results are likely to fall below the normal.

Grant (1934) believes that " flushing " hastens the onset of the breeding season by converting the spurious ovulation periods into true " heat " periods, but he cannot agree that it stimulates earlier production of ripe follicles. Grant contends that " flushing " to be effective must be commenced at least 5 or 6 weeks before the first oestrus is due to occur.

Asdell (1926) cannot agree that increase in feed can be the decisive factor in most animals in determining whether the onset of the sexual season will be early or late, although he considers that the feed supply is certain to have a large influence where the animals are bordering on starvation. The remarks of Clark (1934) appear to agree in principle with the contentions of Asdell.

The effects of mal-nutrition upon the reproductive powers of animals have received some attention; controlled experimentation supports the general contention that underfeeding impairs reproduction.

Observations on laboratory animals indicate that, under conditions of mal-nutrition, the normal functions of the ovaries are affected Leob (1917, *cit.* Marshall, 1922) found that, when guinea-pigs were underfed, maturation is prevented and atrophy takes place; similar treatment in the case of young animals has more marked effects. These results were confirmed by Papanicolaou and Stockard (1920); a prolongation of the dioestrum and a congestion in the uterus and ovary are reported, while the larger follicles were found to be more unfavourably affected by the lack of proper feed.

Marshall and Hammond (1925) consider that mal-nutrition in sheep leads to an increased atrophy of Graafian follicles, which, if excessive, may cause the animals to become sterile for one or more seasons.

Du Toit and Bisschop (1929) give very interesting results in the case of bovines run on mineral-deficient South African veld. When the pasture was balanced by the feeding of bonemeal, 66·1 per cent. of the 109 cows had three calves during three years, whereas none of the 20 controls had three calves during that period. The cows receiving the supplementary mineral in bonemeal produced 87·3 per cent of the possible number of calves, while the equivalent percentage of the control group was 56·5. The authors state that the cows which received bonemeal bred with greater regularity and that cows on deficient pasture exhausted their mineral reserves in the process of gestation and, generally, they needed two or more seasons in order to build up such reserves. Moreover, bonemeal-fed calves out of bonemeal-fed cows, bred earlier in life than did non-bonemeal fed calves out of control cows.

Bekker (1932) has demonstrated the detrimental effects upon reproduction when sheep from phosphorus deficient veld are maintained on a phosphorus deficient ration and that improvement is reflected by adding bonemeal to the ration.

There appears to be some doubt as to whether phosphorus deficiency is the only or the main short-coming in areas where mineral deficiencies are marked. The recent observations of Eckles, Palmer, *et al.* (1935) indicate that irregularities in sexual activity and breeding efficiency are more likely to be due to complicated nutritive deficiencies and not merely to the lack of phosphorus. It was observed that uncomplicated phosphorus deficiency did not cause abnormal oestrous cycles in dairy cows, although such rations did reduce breeding efficiency. The authors reviewed the results of various workers: Hart and Gilbert (1928) consider that the failure of range cows to conceive is in part due to restricted calcium and phosphorus intake, but the lack of protein is also recognised. Gilbert and Hart (1930) found that sexually mature rats on low phosphorus diets showed 80 per cent. cessation of oestrus and 100 per cent. young rats failed to reach sexual maturity on such diets, but it was indicated that the adverse effects were due not merely to phosphorus deficiency, but rather to an abnormally high Ca/P. ratio coupled with low phosphorus intake. Evans and Bishop (1922) demonstrated that protein deficiency decreases the percentage of normal oestrous cycles in rats and that vitamin A deficiency affects the ovulation rhythm. In connection with pasture deficiencies, Hart, Guilbert, and Goss (1932) consider that vitamin A factor may be of considerable importance. However, Theiler (1933) is of the opinion that calcium and vitamin deficiencies are not important factors affecting the fertility of range cattle in phosphorus deficient areas in South Africa, but Hart and Guilbert (1933) considering the symptoms, contend that the lack of vitamin A should have been considered as an important factor of deficiency.

THE PHYSIOGRAPHICAL CONDITIONS UNDER WHICH THE REPORTED OBSERVATIONS WERE MADE.

The experiments were conducted at the Veterinary Research Station, Ermelo, Transvaal. Ermelo is 5,690 feet above sea level. The topography of the district is undulating. The Research Station is located two and a half miles west of Ermelo town. The area of the Research Station is 2,400 acres, which is divided systematically into small camps to permit grazing control. In general, the physiographical conditions of the Research Station may be considered to be fairly representative of a large portion of the eastern Transvaal highveld.

Meteorological Data.

The monthly rainfalls and temperatures of the years during which the experiments reported here were conducted, are given in Table I and illustrated in Diagram 1.

It is apparent from the meteorological records that the rainfall is heaviest during January, February, November, and December; approximately 70 per cent. of the annual rainfall occurs during these months. Although the autumn and winter months are often without rain, very frequently a few inches of rain are recorded. Early spring rains may be expected during August or September. The rainy months are also the hottest months. Very low temperatures are experienced during the winter months. As the accompanying diagram indicates, temperatures are often erratic and frequently comparatively low temperatures are experienced during the autumn and spring seasons.

The Soils.

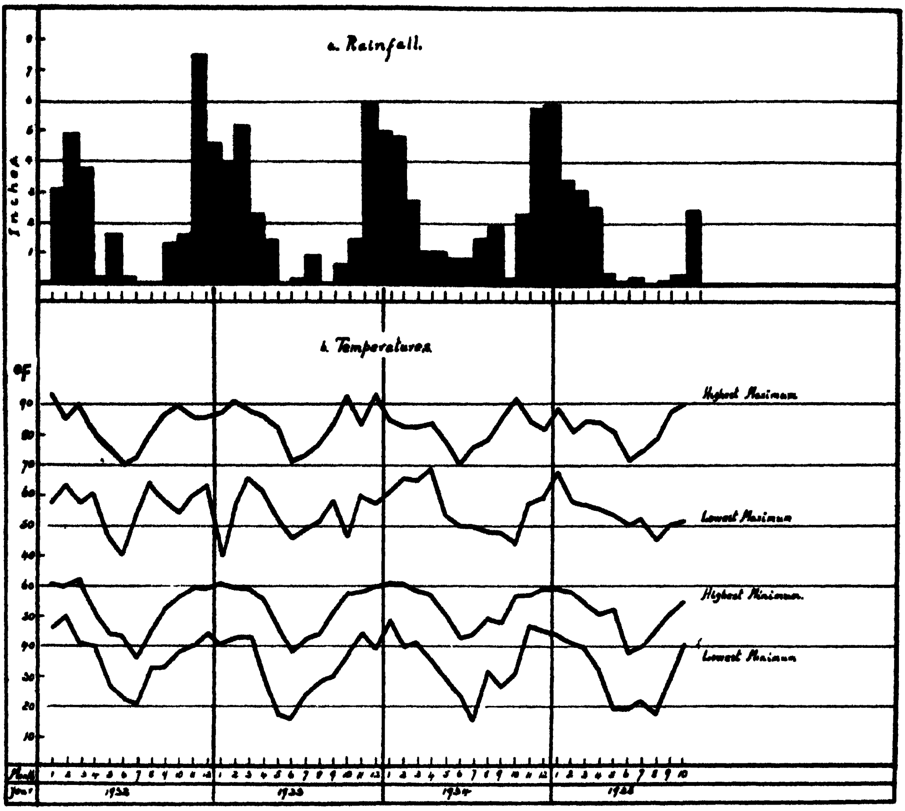
The mineral contents of the main types of soils found on the Research Station have been determined by Henrici [1930 (*a*)] from whose table of results certain data have been extracted and these are presented in Table II.

TABLE I.

Rainfall and Temperature Records: Ermelo.

Year................	1932.					1933.					1934.					1935.				
Month.	Total rain-fall.	High-est max.	Low-est max.	High-est min.	Low-est min.	Total rain-fall.	High-est max.	Low-est max.	High-est min.	Low-est min.	Total rain-fall.	High-est max.	Low-est max.	High-est min.	Low-est min.	Total rain-fall.	High-est max.	Low-est max.	High-est min.	Low-est min.
	Ins.	°F.	°F.	°F.	°F.	Ins.	°F.	°F.	°F.	°F.	Ins.	°F.	°F.	°F.	°F.	Ins.	°F.	°F.	°F.	°F.
January..................	3·06	93·6	58·0	61·0	46·0	3·99	86·8	40·2	61·0	40·3	4·76	85·0	61·4	61·4	49·4	3·41	89·0	68·0	59·0	44·0
February................	4·87	84·8	63·5	59·8	50·0	5·19	91·2	57·4	58·6	42·8	2·68	82·8	66·3	61·0	40·3	3·07	81·0	58·0	58·0	41·0
March....................	3·79	90·0	56·6	62·0	41·4	2·28	88·0	66·4	59·0	43·0	0·98	82·9	65·3	58·9	42·5	2·54	85·0	57·0	54·0	39·0
April......................	0·17	81·0	61·2	51·3	40·0	1·37	85·8	62·2	55·8	29·6	1·02	84·0	69·0	57·0	35·0	0·26	84·0	56·0	51·0	32·0
May........................	1·64	75·2	47·3	44·0	27·4	0·01	81·8	51·9	46·4	17·2	0·83	78·0	54·0	51·0	30·0	0·06	81·0	54·0	52·0	19·0
June.......................	0·25	69·5	40·3	43·3	22·0	0·12	71·3	45·0	39·3	15·3	0·83	70·0	50·0	43·0	24·0	0·20	71·0	50·0	38·0	19·0
July........................	0·00	71·5	52·0	36·0	20·3	0·91	73·2	48·6	43·2	23·2	1·50	76·0	50·0	44·0	15·0	0·03	75·0	53·0	40·0	22·0
August....................	0·00	79·8	63·8	43·6	32·3	0·01	77·4	50·8	44·3	27·5	1·90	78·0	48·0	49·0	31·0	0·10	79·0	45·0	45·0	17·0
September..............	1·32	87·3	58·2	52·0	33·0	0·56	84·1	57·9	51·9	29·5	0·16	86·0	48·0	48·0	27·0	0·30	88·0	51·0	51·0	29·0
October..................	1·62	89·5	53·8	56·3	38·0	1·44	92·7	45·5	58·4	37·0	2·31	92·0	44·0	57·0	31·0	2·38	91·0	52·0	55·0	41·0
November...............	7·46	86·4	59·6	59·2	39·8	5·91	82·9	60·5	58·0	44·0	5·76	85·0	58·0	57·0	47·0	—	—	—	—	—
December...............	4·55	86·4	64·3	59·0	44·5	5·03	92·6	57·1	59·5	39·0	5·86	82·0	59·0	59·0	45·0	—	—	—	—	—
TOTALS............	28·73	—	—	—	—	26·82	—	—	—	—	28·59	—	—	—	—	—	—	—	—	—

DIAGRAM 1.



Rainfall and Temperature Records, Ermelo.

TABLE II.

Soils of Nooitgedacht, 10, Ermelo District, Transvaal.
[Henrici, 1930 (*a*).]

	Grey soil.	Dark brown soil.	Black soil.	Red sandy soil.
	Per cent.	Per cent.	Per cent.	Per cent.
CaO	0·05	0·06	0·70	0 07
MgO	0·08	0·08	0·82	0·14
K_2O	0·15	0·27	0·12	0·12
P_2O_5	0·03	0·03	0·03	0·07
Nitrogen	0·078	0·193	0·084	0·090
Available K_2O	0·012	0·007	0·0035	0·0131
„ P_2O_5	0·001	0·002	0·0012	0·0007
„ CaO	0·010	0·016	0·326	0·046
„ MgO	0·009	0·010	0·152	0·027
P.H. value	5·2	5·1	—	—

It is seen that most of the above soils have a low mineral content and that all the soils are poor in available phosphorus.

THE PASTURE.

Although many varieties of grasses are found in the natural pasture, *Themedra triandra* is the characteristic grass of the area, and it appears that a very mixed grass vegetation with little *Themedra* occurs only on the poorer soils [Henrici, 1930 (*a*)]. In spite of a relatively high rainfall, the dominating grasses of the eastern Transvaal never have the same feeding value as the grasses of drier areas such as Bechuanaland, whereas, when compared with the grasses of Great Britain, it must be wondered that deficiency diseases are not more common in these Transvaal areas [Henrici, 1930 (*b*)]. The data presented in Table III have been extracted from the data determined by Hendrici, [1930 (*a*)] upon analyses of grasses on the Research Station.

TABLE III.

Ash and Protein Content of Themedra triandra *in Percentage of Stove Dry Matter.*

Date of sampling.	Organ.	Ash.	Crude protein.	Crude fibre.	CaO.	MgO	Na_2O.	K_2O.	P_2O_5.	Cl.
27. 4.26	Green leaves.......	—	4·9	29·71	0·30	0·33	0·007	0·80	0·183	—
21. 8.26	Brown „	10·88	2·6	—	0·35	0·23	—	—	0·084	0·088
3. 2.28	Green „	9·7	5·74	—	0·42	0·23	0·044	1·98	0·264	0·286
26. 4.28	Green „	7·87	5·9	—	0·47	0·30	0·044	1·98	0·404	0·540
30. 7.28	Brown „	9·31	2·78	—	0·36	0·25	trace	—	0·159	0·000
2.11.28	Green „	8·84	8·57	—	0·51	0·37	0·008	1·42	0·388	0·682

The researches of Henrici [1930 (*a*); 1930 (*b*)] reveal that, with the sole exception of potassium, the minerals important for the sustinance of animal life are deficient in the dominating grasses for the greater part of the year; for only a short time in spring the grasses may be said to be good. Even in January, regardless of rains, the grasses appear to reach a latent stage, but strangely enough recover in February and March by a new type of secondary growth. During the autumn months, the feed value leaches from the plants. The length of the period during winter months when green leaves are entirely absent varies from 30 to 120 days depending upon the climatic conditions and especially the rainfall.

THE METHODS OF SHEEP HUSBANDRY.

The above physiographical conditions necessitate very particular management if sheep farming is to be a success.

During the summer months, healthy sheep attain good condition, but sheep begin to lose condition in the autumn and the loss of weight during the winter months depends upon the severity of the season and the management afforded.

The feeding of mineral licks is essential, although, it may be added, many farmers do not appreciate this fact. Various combinations usually consisting at least of bonemeal and salt are fed. When licks are self-fed throughout the year, sheep consume larger quantities during the winter months.

In the great majority of cases, it is necessary to supply supplementary feed during the winter months. Some farmers trek with all or most of their sheep to the low veld, where better winter grazing is available. When sheep are wintered on the highveld, the supplementary feeds used are maize and green cereal grazing. The extent of feeding necessary depends upon: the quality and quantity of the available natural pasture, and the type of sheep (old or young, pregnant or non-pregnant, lactating or dry). While a large percentage of dry sheep may be carried through the winter on maize feeding, young sheep up to the age of 18 months, and pregnant and lactating ewes require green grazing for a portion of the winter at least. Provided grain feeding is started before the sheep have lost heavily in condition, from 4 to 6 ounces of maize should assist in maintaining a satisfactory winter weight.

High temperatures and rainfall during the summer months are favourable conditions for internal parasites. When sheep are kept on low-lying pastures, clean drinking water is not supplied, and worm control is not practised, no success with sheep may be expected. The control of internal parasites is essential especially during the first twelve months of the sheep's life.

Due to the difficulty of rearing a satisfactory percentage of healthy sheep, autumn lambing is preferred to spring lambing, as lambs born during the autumn are well advanced when worm infection is likely to be at its worst. Some farmers practice both autumn and spring lambing, but there appears to be some doubt as to whether all ewes can be made to lamb during the former season.

The above conditions were borne in mind when the experiments reported here were planned and the experience in handling the Research Station's available flock was, to some extent, a guide in selecting the rations for the experimental groups.

PART I.

SEX PHYSIOLOGY OF THE NON-PREGNANT EWE.

The various phases of the study are presented as separate experiments.

Certain experiments, and, in certain instances, portions of the same experiment, were commenced at a later date than others. This was necessitated partly by the unavailibility of sufficient sheep material, and also by the difficulty of accommodating very large numbers of sheep in the feed-yards and on suitable representative grazing near the yards. On the other hand, certain additions to the studies were suggested as the investigations progressed.

EXPERIMENT 1.

The Influence of Nutrition upon the Sexual Activity of Non-pregnant Merino Ewes.

Küpfer's (1928) observations on Merino sheep under western Free State (South Africa) conditions, reveal the existance of restricted annual sexual activity in that breed, and he considers that, as Merinos in Australia (Marshall, 1922) and the sheep of Central Europe (Küpfer, 1928) experience unrestricted annual sexual activity, sheep under South African conditions have adapted their ovarian functions to the environment. In other words, the short period of sexual activity of sheep under South African conditions is an adaptation to the conditions necessary for the rearing of the offspring.

The observations of Quinlan and Maré (1931) under Karroo (South Africa) conditions, do not confirm those of Küpfer (1928), in that the former authors observed continuous annual sexual activity in Merino sheep, although it is stated that the absence of rain for extended periods adversely effects the grazing and results in irregularity of the dioestrous cycles. These authors are of the opinion that Küpfer's observations must have been made during an exceptional year when sexual activity was particularly low.

Preliminary observations made by the author at the Research Station, Ermelo, confirmed the findings of Küpfer (1928); Merino sheep under eastern Transvaal conditions exhibit restricted annual sexual activity.

The physiographical conditions of the eastern districts of the Transvaal have been discussed in a previous section. Evidence has been given to indicate that the poor fertility of the soil and the low nutritive value of the pastures do not permit these districts to be classed as good sheep country. The reproductive functions of animals were, therefore, suspected to be restricted by factors largely of a nutritional nature.

The liberal feeding of bone meal licks to stock has, for some time, been accepted as an essential farm practice. Sheep kept solely on natural pasture in these areas are unable to maintain normal health; general weakness and anaemia set in and a comparatively large percentage are likely to die during poor seasons. Long severe winters necessitate supplementary feeding; generally maize is fed but cereal winter grazing may be provided, and, during prolonged droughts, teff hay may be used. The feeding of protein-rich concentrates has not received consideration due to the high prices demanded for such feeds.

The object of this experiment was to study the effects of various levels of feeding and different combinations of feeds upon the sexual activity of Merino ewes which are subjected to such treatment for prolonged periods of time.

Materials and Methods.—The sheep used in the experiment were obtained from the Research Station's available flock of Merinos, which is classed annually according to the recognized standards of Merino flock classing, so that the material, which was taken at random from the flock, may be considered representative of a commercial flock. Eighty sheep were used for the observations in Experiment 1A and 50 in Experiment 1B.

In the formation of the groups for any phase of the experiment, the sheep were divided proportionately with respect to age, type, and weight.

All weight records were taken at 14 day intervals after 12 to 14 hours starvation; the sheep were kept in a covered shed at night and weighing was done between 6 and 8 a.m. the next morning.

All the groups were tested for oestrus daily between 6 and 8 a.m., this work was supervised by the stockman assisted by a native. Four to six vasectomised teasers were used with 10 ewes; the former were kept moving among the ewes for 7 to 10 minutes at each testing.

In the case of the dry-lot or non-pasture groups, open yards measuring 8 x 16 yards and devoid of pasture were used; the yards were supplied with hay racks and feed, water, and lick troughs. No grazing was permitted; the sheep left the yards only for fortnightly weighings and the annual shearing. A certain amount of shelter was afforded by tree wind-breaks. Concentrate rations were fed once daily, roughage twice daily, and the licks and water were available at all times.

The groups on natural pasture were grazed on suitable camps near the observation yards; clean trough water and the mineral licks were available in the camps. The groups were brought to the yards daily between 6 a.m. and 8 a.m. for oestrous observations, and at this time certain groups received their supplementary feed according to the plan of the experiment; the latter groups were drafted out by means of a drafting race.

All the concentrates and licks fed were purchased. The teff hay fed was grown on the Research Station; the quality of the hay was good.

All sheep, in the dry-lots and grazing groups received treatment for gastric and intestinal parasites at 28 day intervals throughout the year. Government Wireworm Remedy was used.

The annual inoculation against Bluetongue took place three weeks prior to shearing. The first dipping in an arsenical preparation for the control of keds was given approximately one month after shearing.

The deaths that occurred in the various groups cannot be said to have been due to the treatment to which the sheep were subjected.

Experiment 1A.

Low Planes of Nutrition in Dry-lot compared to Supplemented Pasture.

The experiment was commenced in July, 1932. At this stage of winter, it was found necessary to start supplementary feeding of the Research Station's general flock; the condition of the sheep was therefore, at a winter level.

Previous experience of the Station's pasture had indicated that non-pregnant Merino sheep on dry winter pasture required from 4 to 5 ounces of maize per sheep per day as supplementary feed, and it was estimated that a sheep consumed between 2 and 3 pounds of dry roughage a day. The rations of the dry-lot fed groups were constructed on this basis.

A general outline of the treatments of the groups in this portion of the experiment is given in Table I.

TABLE I.

Groups in Experiment 1A.

Group.	No. of sheep.	Observations commenced.	Treatment.
I	10	24.7.32	Dry-lot: Maize, teff hay, bone meal, and salt.
II	10	24.7.32	Dry-lot: Maize, teff hay, and salt.
III	10	24.7.32	Dry-lot: Maize, cotton seed meal, teff hay, and salt.
IV	10	(1) 24.7.32	Dry-lot: Maize, teff hay, bone meal, and salt
		(2) 2.3.33	Dry-lot: Teff hay, bone meal, and salt.
V	10	24.7.32	Dry-lot: Maize, teff hay, bone meal, and salt.
VI	10	7.10.32	Pasture: Bone meal and salt.
VII	10	7.10.32	Pasture: Maize, bone meal, and salt.
VIII	10	1.5.33	Pasture: Bone meal and salt, and green oat grazing during winter months.

The sheep of Groups I to IV were approximately 22 months old at the commencement of the experiment. As it was suspected that young ewes might be irregular with regard to sexual activity, Group V, consisting of mature ewes, was included. It will be seen that the maize ration of the latter group is an ounce more than that of Group I with which comparisons are to be made. The initial mean weights of the two groups necessitated this difference in the rations.

The treatment of Group IV during the first period of 224 days was similar to that of Group I, but the former group was subjected to a lower plane of nutrition during the second period of 520 days; the alteration in the ration was made at a time when the sheep were exhibiting normal sexual activity.

Group VII was fed maize according to appetite; the consumption varied from 8 to 12 ounces per sheep per day according to the nature of the natural pasture.

Group VIII was drafted on to green oat grazing for one to two hours daily during the periods when natural green pasture was not available. During the winter months of 1933 the oat grazing was not entirely satisfactory, due to adverse weather conditions, but during the 1934 winter months the green cereal grazing was good.

The quantities of feed and lick consumed are given in Table V of the next section.

Results.

The general treatments of Groups I to VIII have been indicated in Table IV of the text. The details of the feed schedule and the quantities of lick consumed are presented in Table II.

With regard to Table II, attention is drawn to the following points: (1)The rations of the dry-lot fed groups remained constant. As the licks were self-fed, the quantities issued were recorded; the above quantities have been computed from the records of the issues.

(2) Group VII was fed maize at the rate of 8 ounces per sheep per day when pastures were good, but, for approximately 90 days during each of the two winter seasons, the daily consumption per sheep was 12 ounces.

(3) The winter period during which Group VIII was given green oat grazing was approximately 90 days.

(4) The impossibility of feeding lick to each of the pasture groups separately necessitates considering an average figure for the groups on pasture.

The weights of individual sheep in Groups I to VIII, which were taken at 14 day intervals, are given in Appendix 1A, Tables I to VIII. The mean weights of the groups at each period are given and these have been used for the construction of Diagram 2A of the text, which illustrates the tendencies of the weights of the respective groups throughout the experiment. Alterations in the numbers of sheep in the groups are indicated in brackets at points on the curves when reductions occurred.

The records of the observations of oestrus of individual sheep are given in Appendix 1A, Tables IX to XVI, from which Tables XVII to XXIV of the appendix have been compiled in order to reflect the seasonal sexual activity and the periodicity of oestrus of the individuals of each group.

TABLE II.

Rations of Groups.

Group.	No. of sheep.	Period.	Type of treatment.	Rations consumed per sheep per 100 days.				
				Maize.	Cotton-seed meal.	Teff hay.	Bone meal.	Salt.
		days.		lb.	lb.	lb.	lb.	lb.
I	10	744	Dry-lot.	25	—	250	2·60	1·3
II	10	744	”	25	—	250	—	1·8
III (*a*)	10	126	”	16·9	8·1	250	—	1·9
(*b*)	9	618	”	16·9	8·1	250	—	1·6
Average (*a*) and (*b*)	—	744	”	16·9	8·1	250	—	1·75
IV 1st period	10	244	”	25	—	250	1·65	0·82
2nd period (*a*)	10	329	”	—	—	300	1·69	0·85
(*b*)	9	191	”	—	—	300	2·61	1·30
Average (*a*) and (*b*)	—	520	”	—	—	300	2·15	1·08
V (*a*)	10	367	”	31·25	—	250	1·29	0·64
(*b*)	9	154	”	31·25	—	250	1·01	0·50
(*c*)	7	223	”	31·25	—	250	1·60	0·80
Average (*a*), (*b*) and (*c*)	—	744	”	31·25	—	250	1·30	0·65
VI (*a*)	10	350	Pasture	—	—	—	2·32	1·16
(*b*)	9	408	”	—	—	—	2·32	1·16
Average (*a*) and (*b*)	—	758	”	—	—	—	2·32	1·16
VII (*a*)	10	578	”	50·0	—	—	2·32	1·16
(*b*)	10	180	”	75·0	—	—	2·32	1·16
Average (*a*) and (*b*)	—	758	”	62·5	—	—	2·32	1·16
VIII (*a*)	10	369	”	—	—	—	2·32	1·16
(*b*)	10	180	Pasture and oat grazing	—	—	—	2·32	1·16
Average (*a*) and (*b*)	—	549	”	—	—	—	2·32	1·16

It will be observed that dates of slaughter are given in the former tables. The sheep were slaughtered for the examination of the ovaries the reports of which are given in this thesis (Experiment 2: The Morphology of the Ovaries of Merino Sheep during Anoestrum).

Table XXV of Appendix 1A has been constructed from Tables XVII to XXIV in order to obtain the frequencies of the periodicity of oestrus of each of the eight groups.

The following Table III of the text has been compiled from Tables XVII to XXIV of Appendix 1A, in order to permit a comparison of the groups with respect to sexual activity.

An analysis of the periodicity of oestrus made from Table XXV of Appendix 1A is given in Table IV of the text; the two complete sexual seasons of 1933 and 1934 have been considered in the analysis.

The effects of the various treatments upon the wool growth are, to an extent, unrelated to the main purpose of the experiment, but, as the Merino is primarily a wool producing sheep, the shearing results recorded ,although not complete from a wool specialist's point of view, cannot be considered entirely irrevelant to the present study. It was thought that the collection of shearing results might suggest nutritional problems relative to wool growth. The shearing data of the groups have been presented in average figures in Table V of the text. It must be pointed out that, in the case of Groups I to V, only four months of wool growths shorn in 1932 were grown under experimental conditions; in the case of Groups VI and VII, the sheep were drafted into the experiment one month before the 1932 shearing; while, in the case of Group VIII, the sheep were in the experiment for seven months before the 1933 shearing took place.

Photographs of the eight groups of sheep are given in Figs. 1-16.

Discussion.

Few observations upon the sexual activity of sheep have been of long duration; studies with Merino sheep have been continued over periods of 6 and 7 months only (Küpfer, 1928; Quinlan and Maré, 1931).

Little or no attention has been paid to the condition or body weight of sheep in relation to ovarian activity; generally, regular or irregular sexual activity is attributed to good or bad seasons respectively. In sheep husbandry, it is contended that ewes should " pick up " in weight some weeks prior to the mating period, and the practice of " flushing " sheep in order to increase ovarian activity and consequently fertility, is considered to be effective (Marshall, 1903, 1922; Potts, 1924; Marshal and Hammond, 1926). In this connection, the opinion of Asdell (1926) is interesting: He contends that increase of feed is not a decisive factor, although feed supply is certain to have a large influence where the animals are bordering on starvation. The remarks of Clark (1934) appear to agree in principle with those of Asdell.

TABLE III.

The Sexual Seasons.

Group.	Sexual Season, 1932 (*a*).			Anoestrous Period, 1932–1933.			Sexual Season, 1933.				
	No. of sheep.	No. of sheep exhibiting oestrus.	Total No. of dioestrous cycles.	No. of sheep.	Duration.		No. of sheep.	No. of sheep exhibiting oestrus.	Mean No. of dioestrous cycles.	Duration.	
					Range.	Mean.				Range.	Mean.
					days.	days.				days.	days.
I..........	10	2	4	10	182–235	209·5	10	10	8·1	58–217	136·1
II..........	10	1	1	10	172·248	213·6	10	10	6·9	1–207	120·0
III..........	10	0	0	9	199–273	228·0	9	9	4·2	1–163	84·7
IV..........	10	4	7	10	129–218	189·2	10	10	8 9	36–227	158·5
V..........	10	10	28	10	68–210	129·7	9	9	10·7	137–289	217·6
VI........	—	—	—	10	125–157	139·7	10	10	8·8	107–196	154·0
VII........	—	—	—	10	99–180	133·1	10	10	8·9	99–246	179·3
VIII......	—	—	—	—	—	—	10	10	6·1	36–138	91·9(*b*)

Group.	Anoestrous Period, 1933–34.			Sexual Period, 1934.					Anoestrous Period, 1934–1935 (*a*).	
	No. of sheep.	Duration.		No. of sheep.	No. of sheep exhibiting oestrus.	Mean No. of dioestrous cycles.	Duration.		No. of sheep.	Range of period of duration from end of sexual season to date of slaughter.
		Range.	Mean.				Range.	Mean.		
		days.	days.				days.	days.		days.
I..............	10	201–389	276·6	10	9	5·8	21–286	118·1	10	0–154
II..............	10	211–458	294·4	10	9	4·7	35–174	117·2	10	92–164
III..............	9	250–443	333·3	9	8	3·2	1–142	62·9	9	57–161
IV..............	9	125–353	298·8	9	7	2·9	1–117	43·0	9	66–204
V..............	7	178–411	269·4	7	5	7·4	62–185	101·6	7	52–156
VI..............	9	118–341	204·4	9	9	9·2	102–244	183·2	9	68–198
VII..............	10	107–404	180·4	10	10	9·3	1–291	199·1	10	32–122
VIII..............	10	107–231	164·9	10	10	13·3	154–280	230·4	10	38–163

NOTE :—

(*a*) As observations were commenced at the end of the first sexual season (1932) and observations were terminated before the end of the last anoestrous period (1934–1935) by slaughtering, these periods are incomplete, and they are, therefore, not presented in detail similar to that of the intermediate periods.

(*b*) In the case of Group VIII, oestrous observations were commenced on 1.5.33 or about three months after the commencement of the sexual season, 1933.

(*c*) Incomplete periods due to death have not been considered when computing the mean values.

(*d*) The mean duration of the sexual season has been computed by considering only the number showing oestrus, so that sheep present in a group which did not show oestrus have not been considered in the calculations.

TABLE IV.

The Periodicity of Oestrus.

Group.	Sexual Season, 1933.				Sexual Season, 1934.				Sexual Seasons, 1933 and 1934.		
	No. of sheep.	Total number of inter-oestrous periods.	Range of periods after which oestrus recurred.	Percentage cases in which oestrus recurred after a period of 16–19 days (*a*).	No. of sheep.	Total number of inter-oestrous periods.	Range of periods after which oestrus recurred.	Percentage cases in which oestrus recurred after a period of 16–19 days.	Total number of inter-oestrous periods.	Range of periods after which oestrus recurred.	Percentage cases in which oestrus recurred after a period of 16–19 days.
			days.	per cent.			days.	per cent.		days.	per cent.
I..........	10	71	15–82	90·1	10	49	12–72	79·6	120	12–82	84·8
II..........	10	59	15–52	83·0	10	38	16–157	71·0	97	15–157	77·0
III..........	9	29	15–66	55·2	9	18	16–54	50·0	47	15–66	52·6
IV..........	10	79	15–57	83·5	9	13	16–67	84·6	92	15–67	84·0
V..........	9	89	16–68	77·5	7	32	15–145	75·0	121	15–145	76·2
VI..........	10	78	16–36	85·9	9	73	16–100	79·4	151	16–100	82·6
VII..........	10	79	15–105	81·0	10	83	13–84	74·7	162	13–105	77·8
VIII..........	10	51 (*b*)	15–37	90·2	10	122	15–46	91·0	173	15–46	90·6

*NOTE.—(*a*) In a very small percentage of cases oestrus recurs after 15, 20, 21 or even 22 days. For the present purpose the period 16 to 19 days may be considered the normal period after which oestrus recurs.

(*b*) In the case of Group VIII oestrous observations were commenced during the sexual season 1933.

TABLE V.

Shearing Data.

Group.	Average grease wool yields (lb.).			No. of sound fleeces.			Average fleece lengths (inches).		
	1932.	1933.	1934.	1932.	1933.	1934.	1932.	1933.	1934.
I....................	7·5 (10)	7·9 (10)	5·6 (4)	9	8	3	—	2·35	2·50
II....................	7·8 (10)	4·9 (5)	4·9 (5)	8	8	5	—	2·40	2·10
III....................	8·4 (10)	8·7 (9)	— (0)	10	9	—	—	2·60	—
VI....................	7·0 (10)	6·2 (10)	— (0)	8	10	—	2·42	2·40	—
V....................	7·6 (9)	6·6 (8)	4·6 (4)	9	7	4	—	2·20	1·50
VI....................	7·9 (10)	7·8 (9)	5·8 (9)	6	7	8	—	2·30	1·90
VII....................	8·2 (10)	10·3 (10)	7·0 (8)	8	10	8	—	2·68	2·34
VIII....................	—	9·4 (10)	7·2 (10)	—	10	5	—	2·48	2·00

NOTE.—(*a*) The numerals in brackets under the heading "Grease wool yields," indicate the number of sheep in the groups at the particular annual shearing. These numbers are not repeated in the remaining columns.

(*b*) As many sheep were slaughtered prior to the 1934 shearing, the numbers in certain groups are considerably reduced.

Researches upon laboratory animals indicate that deficient rations affect the normal cyclical changes in the ovary (Leob, 1917, *cit.* Marshall, 1922); Papanicolaou and Stockard, 1920; Evans and Bischop, 1922; Gilbert and Hart, 1930). Du Toit and Bisschop (1929) have observed reduced fertility in cattle, and Bekker (1932) in sheep, in phosphorus deficient areas. Eckles, Palmer, *et al.* (1935) consider that irregularities in sexual activity are due not alone to phosphorus deficiency, but to more complex nutritive deficiencies. These authors found that, in dairy cattle, uncomplicated phosphorus deficient rations do not cause abnormal oestrous cycles, although such rations do reduce the breeding efficiency. The following appear to be the most important considerations in deficient rations: low phosphorus, high Ca/P ration coupled with low phosphorus, low protein, and lack of vitamins.

The observations reported in this experiment were conducted over periods of from 549 to 744 days.

Unfortunately, data upon the digestible nutrients of South African feed-stuffs are not obtainable, so that a detailed reflection of feed nutrients available to the groups of sheep under controlled feeding cannot be given. It would be incorrect to compute the nutritive values of the particular rations upon the basis of such standards as that of Henry and Morrison (1923), and to compare the quantities obtained with those considered to be the requirements of "fine wool sheep". The composition of American and South African feed-stuffs vary considerably (Vipond, 1914), and animals under such vastly different conditions may be expected to differ in their nutritional requirements. However, Table XXVI of Appendix 1A gives the analyses of the feeding-stuffs used in this and other experiments reported upon in this thesis.

The growth curves in Diagram 2A., constructed on the mean weights, illustrate the ability of the rations of Groups I to IV to maintain the weights of the sheep at a level approximating those at the commencement of the experiment. It has been explained that the latter weight was a winter weight, one at which, under practical conditions, supplementary feeding of sheep on veld should commence.

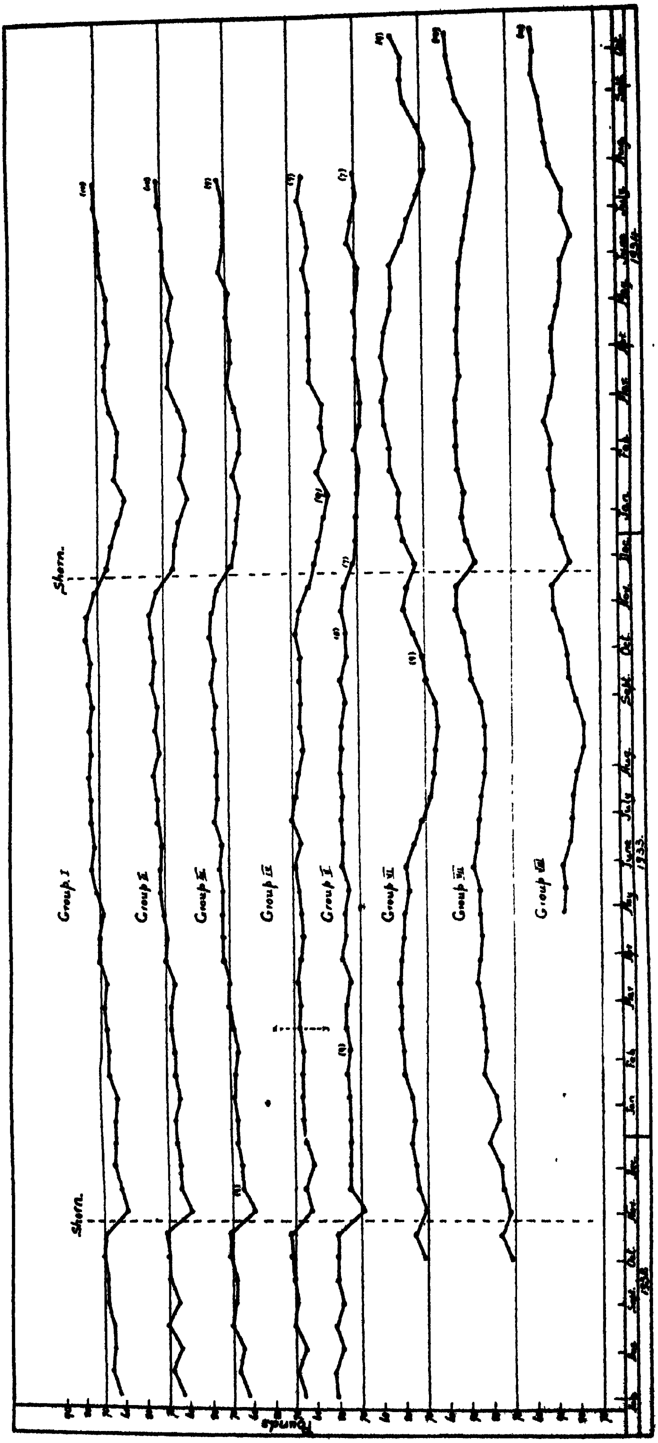
With the exception of Group IV, there is an insignificant difference between the mean weights just prior to shearing in 1932 and 1933. This is also true of the post-shearing weights of those years. It is evident, therefore, that the slight upward trend of the curves is due to wool growth. In Group IV there is a greater tendency to maintain weight in spite of wool growth, hence body weight could not have increased during that period.

Groups I to IV show a decrease in weight just prior to the 1933 shearing. This is considered to be the effect of inoculation upon sheep maintained at a low level weight for an extended period. The decrease is more marked among the weakest sheep of Group IV.

After the 1934 shearing. Groups I to IV show more reluctance to recover weight than was the case during the equivalent time of the previous year. Again, this is more marked in the case of Group IV.

DIAGRAM 2A.

EXPERIMENT 1A.



Mean weights of groups at 14 days intervals.

The three curves of Groups I, II, and III are almost parallel and, considering the rations of these groups (Table II), it may be said that the addition of bonemeal to the salt lick and the inclusion of a protein rich concentrate in the ration, reflects no improvement in body weight when a low level ration of maize, teff hay, and salt lick are fed. On the other hand, the removal of the maize from a low level ration of maize, teff hay, bone meal, and salt, as in Group IV, eliminates the gradual increase evidenced in the preceding groups (Diagram 2A, x-y); the graph of the former group tends to remain horizontal

The older sheep in Group V, on a similar ration to that of Group I, show great consistency in weight, and there is evidence that wool production in such sheep suffers, possibly in order that the reduced body weight may be maintained (Table V).

The weight curves of the veld Groups VI, VII, and VIII, reflect the reaction of the sheep to the altered conditions of the seasons.

The impossibility of having a control group in the true sense of the term has been explained. Group VI on veld supplemented throughout the year only with a mineral lick of two parts of bone meal and one part of salt, must be accepted as a control. Group VI attains its highest summer weight during February and March and it drops to its lowest winter weight during August. The losses in mean weight during the two years are 22·2 and 25·3 per cent. of the highest mean summer weights. The mean highest summer weight during the better season (1934) is 6 pounds greater than that of the preceding season.

The effects of feeding a supplementary ration of maize throughout the year are reflected in the weight curve of Group VII. In this case, the differences between the highest summer and lowest winter mean weights are 5·8 and 10·7 per cent. of the former.

Supplying green cereal grazing when natural green grazing is no longer available, does not entirely eliminate the reaction to winter conditions. Hence, in the case of Group VIII, the differences between the highest summer and lowest winter mean weights are 11·6 and 15·0 per cent. of the former.

With regard to the above computations of summer and winter differences, it must be pointed out that the increase of wool weight during the period of about 6 months which amounts to from 3 to 5 pounds (Table V), has not been considered.

The mean weights of Groups I to VIII at critical periods are given in Table VI of the text.

The critical periods are those at which the mean weights of the veld groups are highest (during February and March) and lowest (during July and August). In the non-veld or dry-lot fed groups, these seasonal differences are not apparent; in these cases differences in weight are due to wool growth. The weights at the critical periods are of particular interest in connection with seasonal activity and reference will be made to these weights in subsequent discussions.

TABLE VI.

Mean Weights at Critical Periods.

Group.	1932.		1933.				1934.			
	July, 22.	Aug., 20.	Feb., 1.	Mar., 30.	July, 21.	Aug., 31.	Feb., 1.	Mar., 16.	July, 21.	Aug., 18.
	lb.	lb.	lb.	lb.	lb.	lb.	lb.	lb.	lb.	lb.
I..............	61·4	63·2	65·0	66·1	72·4	73·2	61·4	62·1	68·7	67·4
II..............	61·4	62·4	64·3	64·6	71·6	72·8	59·0	60·6	68·7	67·3
III............	61·2	63·4	66·8	69·6	73·4	75·2	64·9	64·4	68·9	69·3
IV............	65·6	64·9	65·5	68·0	67·2	65·9	56·3	63·6	63·7	59·2
V..............	80·4	77·4	75·7	73·9	76·3	76·6	69·9	67·1	67·8	66·9
VI............	—	—	80·4	82·2	67·4	63·3	83·8	87·4	69·4	64·8
VII............	—	—	83·4	86·2	82·8	82·3	92·8	93·0	83·6	82·6
VIII..........	—	—	—	—	81·4	75·6	91·4	90·0	83·4	89·5

In Groups I to V, oestrous observations were commenced during the latter part of the sexual season of 1932, in Groups VI and VII approximately 5 weeks after the termination of the sexual season of 1932, and in Group VIII approximately three months after the commencement of the sexual season of 1933 (Appendix 1A, Tables IX to XVI and Tables XVII to XXIV). Oestrous observations in all groups terminated during the anoestrous period of 1934-1935. Two complete sexual seasons of 1933 and 1934 were included in the studies of all groups with the exception of that of Group VIII.

The results of the extensive oestrous observations indicate that, under eastern Transvaal conditions, Merino sheep of various ages which have been subjected to the treatments indicated, experience restricted annual sexual activity. It may be said that the sexual season commences in February and terminates in August, although the duration of the sexual season of certain individuals extends beyond these limits (Appendix 1A, Tables IX to XVI). It is to be noted that, in the case of the veld groups which react in body weight to the altering conditions of the seasons, sexual activity increases when body weight decreases during the autumn and early winter months, and that, while body weight increases rapidly during the spring and early summer months, sexual activity is absent. In the case of the controlled fed groups in which very little or no gain of body weight is reflected, the rhythm of the sexual seasons corresponds to that of the former groups. (Table VI and Diagram 2A).

A conception of the great variation of the extent of sexual activity of individuals in all groups can be obtained by consulting Tables XVII to XXIV of Appendix 1A. While certain members of a group exhibit the ultimate degree of sexual activity expected, others experience no activity or only 1, 2, or 3 dioestrous cycles during a sexual season. By consulting the weights of indivadual sheep (Appendix 1A, Tables I to VIII), it becomes apparent that the heaviest sheep of any group are not necessarily the most active, nor are the lightest the least active.

Individual differences of sexual activity are greater in the groups of young sheep, Groups I to IV, on low level rations, and such differences become greater during the second sexual season on such rations. Attention is drawn to Sheep No. 29324 which exhibited a continuous series of regular dioestrous cycles from the beginning of April, 1934, to the middle of January, 1935 (Appendix 1A, Table IX). In the more mature sheep on a low level ration, individual differences are marked only during the second sexual season.

In the case of the sheep on veld (Group VI), individual differences are less marked than in the case of the groups on low level rations, and, while such differences are not increased during the second sexual season, the least active sheep during the first season are also least active during the second season. Greater individual variation occurs in the group of sheep on veld supplemented with maize throughout the year. Three sheep in this group experienced exceptionally short anoestrous periods during the spring of 1934 (Appendix 1A, Table XV). In this case too, the least active during the first season are least active during the second sexual season. The two least active sheep are not exceptionally heavy or exceptionally light in body weight (Appendix 1A, Table VII). In the case of Group VIII, which was permitted green grazing throughout the year, a certain amount of individual variation occurs during the first season, but such variation is considerably reduced during the second season and, in this case, the activity of the least active sheep during the first season excels that of others during the second sexual season. One sheep in this group experienced a relatively short anoestrum during the spring of 1934 (Appendix 2A, Table XVI).

Group summaries of the sexual seasons are contained in Table III of the text.

The sheep in Groups I to IV were 22 months old when they were drafted into the experiment towards the end of the sexual season of 1932. It is apparent from Table III that the greater percentage of these sheep were sexually inactive during the latter part of the 1932 sexual season. It will be shown in a subsequent experiment that only 20-40 per cent. of Merino sheep at 18 to 23 months of age experience sexual activity under eastern Transvaal conditions (Experiment 6). It is seen that 100 per cent. of the mature sheep in Group V exhibited oestrus during the latter part of the 1932 sexual season.

The mean duration of the true anoestrous period is reflected only in the case of Group V, in which all sheep were observed to have been sexually active during part of the preceding sexual season (1932). However, from the few cases in Groups I to IV that can be used for a comparison, it appears that the anoestrous period at the commencement of the experiment was longer in the younger sheep than in the mature sheep of group V, the mean duration of the anoestrous period of which was approximately 130 days. As the observations on Groups VI and VII were commenced when all the sheep were in anoestrum, the periods of duration of the 1932-1933 anoestrous period cannot be used for comparative purposes, although they indicate the total absence of oestrus for the given lengths of time (Table III).

Significant comparisons may be made from the time of the onset of the 1933 sexual season up to the termination of the 1934 sexual season (Tables III and IV of the text).

1. The results obtained from Groups I and II reveal the following:—

(*a*) During 1933, the mean duration of the sexual season of Group I is 16·1 days longer than that of Group II; in the latter group cases of extreme short duration of the season occur. During 1934, the mean durations of the sexual seasons are almost identical, although the range of variation is greater in the case of Group I.

(*b*) The mean numbers of dioestrous cycles in Group I during the sexual seasons of 1933 and 1934, exceed those in Group II by 1·2 and 1·1 respectively.

(*c*) During the 1933 and 1934 sexual seasons, the cases in which oestrus recurs after the normal period of 16 to 19 days, is greater in Group I by 7·1 and 8·6 per cent. respectively.

(*d*) The mean anoestrous period (1933-1934) of Group I is 17·8 days shorter than that of Group II.

(*e*) Both groups show decreased sexual activity during the second season.

2. When a portion of the low level maize ration is replaced by a protein rich concentrate, cottonseed meal, as in Group III, the results as compared to Groups I and II reflect marked reductions in sexual activity:

(*a*) The mean durations of the 1933 and 1934 sexual seasons are reduced by 51·4 and 55·2 days respectively as compared to Group I and by 35·3 and 54·3 days respectively as compared to Group II.

(*b*) The mean number of dioestrous cycles during the sexual seasons of 1933 and 1934 are reduced by 3·9 and 2·6 respectively as compared to Group I and by 2·7 and 1·5 respectively as compared to Group II.

(*c*) During the 1933 and 1934 sexual seasons, the cases in which oestrus recurs after the normal period of 16-19 days are 55·2 and 50 per cent. respectively as compared to 90·1 and 79·6 per cent. in Group I and 83·0 and 71·0 per cent. in Group II.

(*d*) The mean anoestrous period (1933-1934) of Group III is of longer duration than that of Groups I and II by 56·7 and 38·9 days respectively.

(*e*) A marked decrease in sexual activity occurs during the second sexual season.

3. When the maize ration is withdrawn from a low level ration of maize, teff hay, bone meal, and salt, after a period of 224 days, as in Group IV, no immediate detrimental effects upon sexual activity result, but marked reductions in activity are evidenced during the next sexual season:

(*a*) The mean duration of the 1933 and 1934 sexual seasons are 158·5 and 43·0 days respectively, the longest duration during the latter sexual season being only 117 days.

(*b*) The mean number of dioestrous cycles is 8·9 during 1933 and only 2·9 during the 1934 sexual season.

(*c*) Considering the two sexual seasons, there is no significant difference between the percentage of cases in which oestrus recurs after the normal period of 16 to 19 days; the percentages are 83·5 and 84·6 respectively.

(*d*) The mean duration of the 1933-1934 anoestrous period is 298·8 days which is 22·2 days in excess of that of Group I and approximately of similar duration to that of Group II.

(*e*) As a result of the withdrawal of the maize portion of the low level ration, sexual activity is greatly reduced during the second sexual season.

4. The results obtained from Group V may be compared with those of Group I, as the treatments of the groups were similar. The sheep comprising Group I were 22 months old at the commencement of the experiment, while the sheep of Group V were mature.

(*a*) The mean duration of the 1933 sexual season is 81·5 days longer in the case of the mature sheep, but the duration of the second sexual season is reduced by 116 days compared to the previous season. The reduction is greater than in the case of the younger sheep.

(*b*) The reduction of the mean number of dioestrous cycles of the mature sheep is from 10·7 to 7·4 during the sexual seasons of 1933 and 1934 respectively. On a percentage basis this reduction is approximately equal to that experienced by the younger sheep in Group I.

(*c*) The number of cases in which oestrus recurs after the normal period of 16 to 19 days is 77·5 per cent., which is 12·6 per cent. less than in the younger sheep. However, during the second sexual season, the percentage is insignificantly less in the case of the mature sheep, but it is significantly reduced in the case of the younger sheep.

(*d*) The mean anoestrous period (1933-1934) of the mature sheep is only 7.2 days less than that of the younger sheep.

(*e*) A marked decrease of sexual activity of the mature sheep occurs during the second sexual season; reduced activity is due largely to the shorter duration of the sexual season.

5. The sheep comprising Group VI were maintained on natural pasture supplemented only by bone meal and salt. The results obtained from this group will be compared with those of the dry-lot groups, and comparisons with the other veld groups will be made when the results of the latter are being considered.

(*a*) The mean duration of the 1933 sexual season of Group VI is 63·6 days less than the longest sexual season of the dry-lot groups on low level rations. No explanation can be found for this difference. The mean duration of the second sexual season of Group VI is 63·5 days longer than the longest sexual season of the groups on low level rations. The mean duration of the second sexual season (1934) of Group VI is 29·2 days longer than the previous season. This difference is due to the extension of the latter part of the season (Appendix 1A, Table XIV), and, while no exact explanation can be offered for this extension of activity, it must be remarked that abnormally good rains were experienced during the winter and early spring months of 1934 (Diagram 1) and that good sheep pasture was available by the middle of August, 1934.

(*b*) The mean number of dioestrous cycles of the veld group during the 1933 sexual season is approximately equal to that of sheep on a low level ration of maize and teff hay. The mean number of dioestrous cycles of the veld group is increased during the second sexual season, while those of the groups on low level rations are decreased.

(*c*) The number of cases in Group VI in which oestrus recurs after the normal period of 16 to 19 days is 85·9 and 79·4 per cent. during the sexual seasons of 1933 and 1934 respectively. These percentages are greater than in most low level ration groups.

(*d*) The mean anoestrous period (1933-1934) of the veld group is 204·4 days, which is shorter than any of that of the low level ration groups.

(*e*) Increased sexual activity during the second sexual season is shown by the veld group; this is due largely to the longer duration of the sexual season.

6. The results obtained by constantly supplementing natural pasture with maize, as in Group VII, are best compared with those of the veld group, Group VI.

(*a*) The mean duration of the 1933 sexual season of Group VII is 25·3 days longer than that of Group VI, but the 1934 season of the former group is only 15·8 days longer than that of the latter group. The mean duration of the second season in the case of Group VII is greatly influenced by a particularly inactive individual.

(*b*) There is no significant difference between the mean number of dioestrous cycles of Groups VI and VII during both sexual seasons.

(*c*) The percentage of cases in which oestrus recurs after the normal period of 16 to 19 days is somewhat larger during both seasons in the case of Group VI.

(*d*) The mean anoestrous period (1933-1934) of Group VII is 24 days shorter than that of Group VI.

(*e*) As in Group VI, the sexual activity of Group VII increases during the second sexual season.

7. The results obtained by supplying green feed to sheep throughout the year, as in Group VIII, may be compared with those in which no supplementary feed is given, as in Group VI, and in which natural pasture is supplemented throughout the year with maize, as in Group VII.

(*a*) Oestrous observations on Group VIII were commenced on 1.5.33, or approximately three months after the onset of the sexual season. In spite of this, the mean duration of the 1933 sexual season is 91·9 days. The mean durations of the equivalent periods of the 1933 sexual season have been computed for Groups VI and VII, and they are found to be 87·2 and 86·4 days respectively. The mean duration of the 1934 sexual season of Group VIII is 230·4 days which exceeds that of Group VI by 47·2 days and that of Group VII by 31·3 days.

(*b*) During the portion of the 1933 sexual season, the mean number of dioestrous cycles experienced by Group VIII is 6·1, while the numbers experienced by GroupsVI and VII during the identical period are 5·6 and 5·2 respectively. During the 1934 sexual season, the mean number of dioestrous cycles is 13·3, which exceeds that of Groups VI and VII by 4·1 and 4·0 respectively.

(*c*) In Group VIII, the percentage of cases in which oestrus recurs after the normal period of 16 to 19 days is approximately 90 and this greatly exceeds the corresponding percentages reflected for Groups VI and VII.

(*d*) The mean anoestrous period (1933-1934) of Group VIII is 164·9 days, which is less than that of Groups VI and VII by 39·5 and 15·5 days respectively.

(*e*) The sexual activity of Group VIII is greatly increased during the second sexual season.

None of the groups subjected to the above treatments experienced a continuous series of dioestrous cycles throughout twelve months. The greatest amount of sexual activity was shown by sheep which were permitted green grazing throughout the year. The supplementary feeding of concentrates (maize) throughout the year to sheep on pasture resulted in some increase of sexual activity as compared with the results from unsupplemented pasture. The sexual activity of sheep on low level or deficient rations declines as the time of treatment advances.

It appears from the literature cited that the extreme degree of polyoestrum is a breed characteristic of the Merino. However, it has not been established what variation of the degree of polyoestrum, due to individual differences within the breed, may be expected under ideal environmental conditions.

Further, evidence available proves that the extent of ovarian activity is influenced by environic factors one of which, namely nutrition, is of great importance.

It is highly probable that sheep are far more sensitive to nutritional deficiencies than is at present realised. While ability to reflect normal body functions under imperfect nutritional conditions for periods of considerable duration, may be an exceptional individual characteristic, it must be realised that the majority of sheep are unable to experience maximum ovarian activity when they are subjected to adverse nutritional conditions, and the reflection of such treatment becomes more marked as time progresses. While in certain areas, the deficiency of the pasture may be due to the lack of one or a few mineral or protein elements, in other areas a more complex deficiency may exist. Although it is contended that farm animals seldom suffer from vitamin deficiency, this fact has not been established for all areas. Vitamins are essential nutrients for all phases of body functions; as Aschheim (1933) points out: " The function of the endocrine glands depends greatly upon the presence of certain vitamins in the diet ".

Conclusions.

1. The effects of various combinations of low level rations upon the sexual activity of Merino sheep were studied. A control group on veld and two veld groups, the grazing of which was supplemented, were used for comparative purposes.

The observations were conducted over periods of from 18 to 26 months.

The recording of weight data indicated the reaction of body weight to the treatment imposed.

2. Irrespective of treatment, Merino sheep under eastern Transvaal conditions experience restricted annual sexual activity. The sexual season commences in February and terminates in August; the anoestrous period embraces the spring and summer months. Great individual differences with respect to degree of polyoestrum are reflected in all groups subjected to the various treatments.

3. Sheep subjected to low level rations of maize, teff hay, and salt, which permit them to maintain a weight approximating that of their winter condition, do not exhibit marked decreased sexual activity during the first 7 to 12 months of treatment, but an abrupt decline in sexual activity results after 19 to 24 months and the reduced degree of activity is influenced by the quality of the ration.

(*a*) The inclusion of bone meal in the salt lick has no significant effect upon body weight and wool production.

The addition of bone meal prevents marked reduction of the duration of the sexual season, the number of dioestrous cycles, and the increase of dioestrous cycles of abnormal duration. However, the inclusion of bone meal in such rations does not ensure normal sexual activity.

(*b*) The part substitution of the maize portion of the ration with a protein rich concentrate (cotton seed meal), has no significant effect upon body weight, but a slight improvement upon wool production.

The alteration results in an earlier decline of sexual activity and a very marked reduction of sexual activity after 18 months of treatment. The sexual season is of shorter duration, the number of dioestrous cycles is less, and the number of dioestrous cycles of normal duration is reduced.

(*c*) The inclusion of bone meal in the ration at the commencement of treatment, and the withdrawal of the maize portion of the ration after a period of approximately 7 months, or one month after the onset of the first sexual season, results in a lower constant weight level and a reduction in wool yield.

The reduction in the ration greatly reduces the duration of the sexual season and the number of dioestrous cycles.

(*d*) The sexual activity of mature sheep on low level rations is not as readily affected as in the case of younger sheep, but, when reduction of activity of the former takes place, it is more marked than in the case of younger sheep.

4. Sheep maintained on natural pasture, react abruptly in body weight and sexual activity to the seasons. The drop in body weight is greatly reduced by supplementary feeding and better wool production results. Increased sexual activity is induced by supplementing the natural pastures; the degree of improvement depends upon the nature of the feed supplied. However, the rhythm of the sexual seasons is maintained irrespective of the treatment.

(*a*) Sheep maintained on natural pasture attain their highest summer weight during February and March and they drop to their lowest weight during August; the loss in weight my be 25 per cent. of the highest summer weight.

The annual wool production may vary by approximately 2 pounds.

The sexual activity varies during different sexual seasons. It may not greatly exceed that of sheep on low level rations for periods of 7 to 12 months, but marked improvement of activity of the former may occur during the next sexual season. Under these conditions of treatment, the duration of the sexual season may be 6 months. The specific factors involved have not been identified, although it may be remarked that greater sexual activity results by the extension of the latter part of the sexual season when good rains are experienced during the winter months.

(*b*) The supplementary feeding of sheep on natural pasture with 8 to 12 ounces of maize throughout the year, does not entirely eliminate the loss in weight during the winter months; losses of approximately 6 and 11 per cent. of the highest summer weight are experienced.

While improvement of wool production may be expected, high yields of good quality are not constant. Other influential factors appear to be involved; these factors have not been identified.

Such feeding tends to increase the duration of the sexual season, but it does not result in lengthy sexual seasons in all individuals. Under these conditions of treatment, the duration of the sexual season may be 6·5 months. The normal periodicity of oestrus is not ensured.

(*c*) When sheep are permitted green grazing throughout the year, the loss in weight during the winter months is reduced to 12 to 15 per cent. of the highest summer weight.

Improvement of wool production results, but high yields of good quality are not constant.

Under such treatment, sheep experience great improvement in sexual activity. The improvement is rapid and it becomes more marked as the period of treatment progresses. The duration of the sexual season is extended; it may be 7·5 months. A significantly larger number of dioestrous cycles is experienced, and, in approximately 90 per cent. of cases, oestrus may be expected to recur after the normal interval.

5. The specific factor or factors which determine the existence of restricted annual sexual activity in Merino sheep under eastern Transvaal conditions have not been revealed by these studies, but the latter suggest that restricted seasonal activity is, to some extent, influenced by nutritional circumstances.

6. While the degree of polyoestrum exhibited during sexual seasons may be influenced by individual differences, it is apparent that nutritional factors play an important rôle. Improved treatment appears to induce greater sexual activity and to shorten the duration of the anoestrous period. Marked stimulation of ovarian activity results by permitting constant green grazing; this fact suggests the importance of the essential vitamins.

7. Sheep maintained on deficient rations for long periods of time suffer from complicated nutritive deficiency which inhibits normal ovarian activity. The availability of adequate quantities of phosphorus in the form of bone meal lick, does not result in normal sexual activity.

Experiment 1B.

High Planes of Nutrition in Dry-lot compared to Supplemented Pasture.

The results obtained from the observations in Experiment IA, indicated the need for studying the sexual activity of Merino sheep under the same climatic conditions when high planes of nutrition are allowed. Also, the exceptionally poor results reflected by sheep the ration of which contained cotton seed meal (Experiment 1A, Group III), suggested the inclusion of tests upon the more commonly used protein rich concentrates such as: cotton seed meal, peanut meal, and blood meal. It may be said that information relative to the value of these protein rich concentrates is of particular interest to stud owners in areas where leguminous roughages cannot be grown with success, and where non-nitrogenous roughages and concentrates are the farm feeds most successfully produced.

The experiment was commenced on November 5th, 1934, and the results of 12 months are available. It may be said that it is in the interests of the experiment to extend the observations over a further period of at least 12 months; these results will be published in a subsequent issue of the Onderstepoort Journal.

The following general outline indicates the plan of the experiment: —

(*a*) The feeding of maize with teff hay and a salt lick.
- (1) Group I: no nitrogenous supplement.
- (2) Group II: supplemented by cotton seed meal.
- (3) Group III: supplemented by peanut meal.
- (4) Group IV: supplemented by blood meal.

(*b*) On natural pasture: Group V: supplemented by a bone-meal and salt lick and green cereal grazing during the winter months.

Each of the above groups consisted of ten Merino ewes of good type and approximately three years of age.

The ewes were taken from the Research Station's available flock; consequently, their breeding histories were not known. They were shorn just previous to their inclusion in the experiment, hence their entire wool growth was made during experimental treatment.

As indicated in a previous section (Experiment IA), data upon the digestible nutrients of South African feedstuffs are not available. In consequence, the nutritive requirements of the sheep could not be computed. In the case of Group I, the quantity of maize fed was based upon the reaction to maize feeding reflected in Experiment 1A, Group VII. Although, for reasons previously stated, the digestibility of South African feed-stuffs cannot be accepted to be similar to that of American feed-stuffs, the tables of digestible nutrients given by Henry and Morrison (1923) were the most suitable guide in compiling the concentrate constituents of the rations of Groups II to IV. It was endeavoured to compound the rations so that the crude protein and total digestible nutrients of all rations were as nearly as possible equal. In the case of Group I, the ration of which contained no protein rich supplement, the crude protein content of the ration is low. The following Table I indicates the details of the rations fed to the groups. In connection with the lick consumption, it must be pointed out that the lick was supplied ad lib.

TABLE I.

The Rations.

Group.	Daily ration of concentrates, roughage and lick per sheep per day.						Digestible nutrients in concentrate portion of daily ration.			
	Maize.	Cotton-seed meal.	Pea-nut meal.	Blood meal.	Teff hay.	Salt.	Crude protein.	Carbo-hydrates.	Fat.	Total digestible nutrients.
	oz.	oz.	oz.	oz.	lb.	oz.	lb.	lb.	lb.	lb.
I.......	8	—	—	—	2·5	0·19	0·0385	0·3305	0·2300	0·4210
II......	4	5	—	—	2·5	0·25	0·1172	0·2446	0·0357	0·4424
III.....	5	—	4	—	2·5	0·23	0·1246	0·2412	0·0373	0·4678
IV.....	6	—	—	3	2·5	0·24	0·1606	0·2512	0·0192	0·4550
V......	*6b*	—	—	—	—	0·23	—	—	—	—

All issues of lick were made as required and they were entered on the feed-room record sheet.

Due to the severity of the winter months, Group V could not be given green cereal for two hours daily throughout the winter months, so that it was necessary to resort to supplementing the natural pasture by maize for short periods.

The particulars of the management of Group V are as follows:—

(1) 5.11.34 to 6.5.35 on natural pasture without supplements.

(2) 7.5.35 to 17.8.35: on natural pasture with cereal grazing for 2 hours daily.

(3) 18.8.35 to 4.9.35: on natural pasture with 6 oz. maize.

(4) 5.9.35 to 7.10.35: on natural pasture with cereal grazing for 2 hours daily.

(5) 8.10.35 to 31.10.35: on natural pasture with 6 oz. maize.

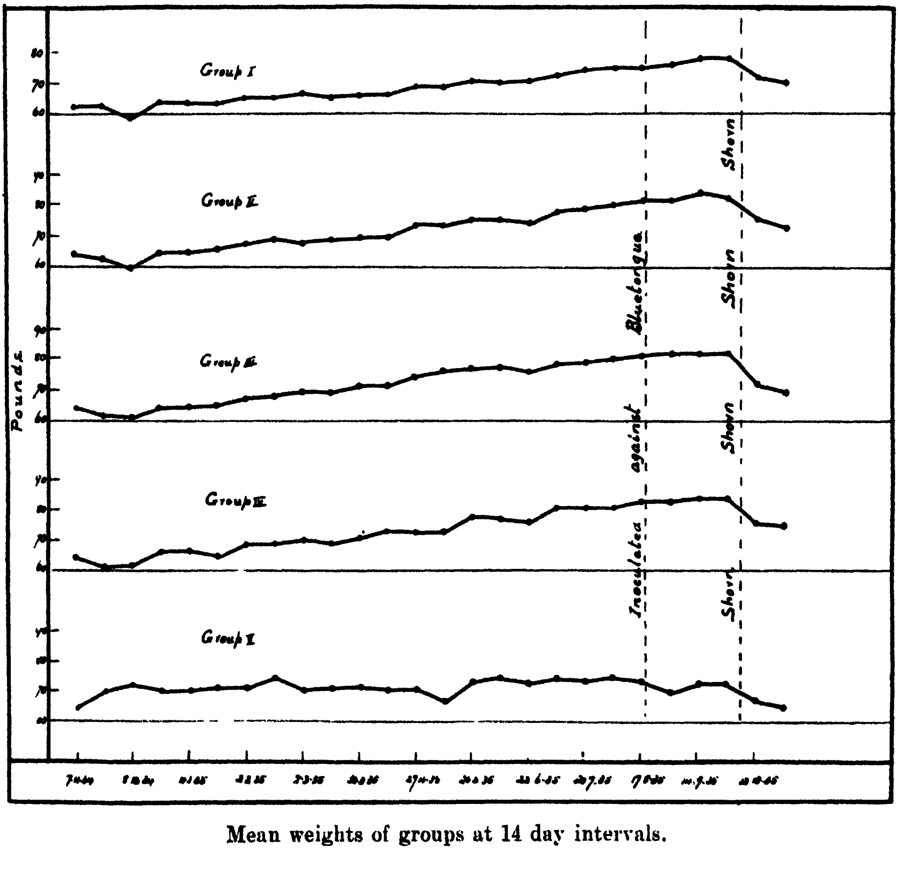
The details of general management of these groups were identical to those of the groups of Experiment 1A, and the methods employed have been given under the section of Experiment 1 dealing with such matters.

Results.

The weight data of Groups I to V, taken at 14-day intervals, are given in Appendix 1B, Tables I to V, from which Diagram 2B has been constructed.

DIAGRAM 2B.

EXPERIMENT 1B.



Mean weights of groups at 14 day intervals.

The results of the oestrous observations on the five groups of sheep are given in Appendix 1B, Tables VI to X. The results obtained from individual sheep have been analysed and the data of interest have been included in the latter tables. These data have been condensed in Table II of the text in order to permit a comparison of the groups.

TABLE II.

The Sexual Activity of Merino Sheep on High Level Rations.

Group	Period between commencement of testing and 1st oestrus.		No. of dioestrous cycles.		Duration of sexual season.	
	Range.	Average.	Range.	Average.	Range.	Average.
	days.	days.			days.	days.
I......	27–172	65·4	2–18	11·2	17–291	186·1
II.....	28– 96	45·5	2–19	11·3	19–304	203·6
III....	30–117	59·2	3–18	12·8	106–314	229·6
IV.....	27– 99	53·1	3–17	10·2	87–295	209·5
V......	42–157	66·1	4–17	10·7	77–290	201·8

Group.	Frequencies of the periodicity of oestrus (days).																													Total.	Period between last oestrus and the termination of testing for oestrus.	
	10	13	14	15	16	17	18	19	20	21	23	24	32	33	34	35	36	37	38	39	47	49	51	52	56	68	70	87	168		Range.	Average.
																															days.	days.
I......	—	—	—	—	17	41	35	4	1	—	—	—	—	—	—	1	2	—	—	—	—	1	—	—	—	—	—	—	—	102	35–172	107·3
II.....	1	1	—	1	11	35	34	5	—	1	1	1	—	—	2	5	1	1	—	1	—	—	—	1	—	—	1	—	—	103	10–174	89·8
III....	—	—	2	3	22	49	21	6	1	—	—	—	2	—	6	3	1	1	—	—	—	—	—	—	—	—	1	—	—	118	17–139	73·2
IV.....	—	1	1	1	8	42	22	3	1	—	—	—	—	—	3	2	1	—	1	—	—	—	1	1	1	1	—	1	1	92	38–248	99·4
V......	—	—	1	—	4	50	18	3	1	2	—	—	—	1	4	4	3	—	—	1	1	2	1	1	—	—	—	—	—	97	8–159	87·3

The shearing results obtained from the groups are given in Table III of the text.

TABLE III.

Wool Production.

Group.	No. of sheep.	Grease wool Yield.		Staple length.		Tensile strength No. of sound fleeces.	Spinning quality frequencies.			
		Range.	Average.	Range.	Average.		60s.	64s.	70s.	74s.
		lb.	lb.	ins.	ins.					
I....	10	5·5– 8·1	7·4	2·00–2·75	2·5	10	—	2	8	—
II...	10	6·6–12·4	9·2	2·50–3·00	2·8	10	—	2	7	1
III..	10	5·5–11·0	8·2	2·25–3·00	2·6	10	—	5	5	—
IV...	10	8·5–11·8	10·0	2·50–3·00	2·8	10	1	9	—	—
V....	10	6·3– 9 7	8·0	2·25–3·00	2·6	10	—	—	9	1

Photographs of the five groups are given in Figures 17 to 21.

Discussion.

The reactions of Groups I to IV to the altered conditions of dry-lot feeding are reflected in the reduction in weights during the first 28 days of the experiment (Diagram 2B). The sheep on pasture, Group V, show an increase in weight during that period; this may be expected of such sheep during November and December of a good sheep year (Diagram 1). During the remainder of the experimental period, Group V maintains a fairly constant mean weight; the temporary abrupt decline early in May is a reaction to the commencement of the winter conditions, but it has been seen that supplementary feeding was started on 7 May, 1935, hence the response to the treatment was immediate. Subsequent slight fluctuations in weight evidenced during the latter part of August may be expected during severe winter conditions. Although Group V attained a maximum mean weight of only 74 pounds, for practical purposes it would be considered that they maintained a satisfactory weight level for normal body function and production. The sheep did not lose weight as was evidenced in the groups on pasture in Experiment 1A (Groups VI and VIII).

The dry-lot fed groups reflect greater gains in weight. Group I, on a maize ration unsupplemented by a protein concentrate, made gradual gains in weight; the levels of 70 and 79 pounds were attained 10 weeks after the protein supplemented ration groups reached those levels, while the mean weight of the former immediately prior to shearing was from 3 to 5 pounds less than that of the latter groups. There is no great difference between the weight curves of Groups II, III, and IV. The group receiving blood meal as a supplement, Group IV, made slightly faster gains during the first six months of the experimental period, but subsequently the weight curves are almost identical, although the group receiving peanut meal as a supplement, Group III, shows a greater tendency to maintain its weight just prior to shearing, and the post-shearing weight of the latter group is 4 pounds less than that of Groups II and IV.

The wool production results (Table III) are of interest, not only from a point of view of the production efficiency of the treatments, but also as they may indicate whether treatment or rations which are satisfactory from a wool production aspect, are as efficient with respect to the functions of the body concerning reproduction.

In spite of the greater body weight gains of Group I as compared to those of Group V, the wool production of the former is below that of the latter in every respect. Obviously, significant differences exist between the wool productions of Groups II, III and IV. The production of Group III is seen to approximate that of the veld group, Group V, although the former contained more fleeces of lower spinning qualities. The wool production of Groups II and IV are considered excellent for sheep of that type; the number of high spinning quality fleeces in Group II and low spinning quality fleeces in Group IV is a point of interest.

It may be said that wool production is improved by the inclusion of cottonseed meal and blood meal in the carbonaceous rations of Merino sheep, while the results obtained by feeding a high level carbonaceous ration are not as satisfactory as those reflected by Merino sheep under good farm veld management.

The details of the results of the oestrous observations and the analyses of these data reveal interesting facts (Appendix 1B, Tables VI to X).

It is obvious that all groups were in anoestrum during November, 1934, not a single occurrence of oestrus was observed during that month.

The sexual season commenced during December and, excluding a small percentage of cases, 8 per cent., the sexual season is restricted. In this connection particular attention is drawn to the marked individual differences which occur in the duration of the sexual season in all groups; while 18 and 19 dioestrous cycles were experienced by certain individuals in the various groups, others in the same groups experienced only 2 and 3 dioestrous cycles. Mention of similar individual differences was made in discussing the results of sheep on low level rations in Experiment 1A.

Table II of the text presents a summary with respect to the sexual activity of the groups.

It is seen that the group on a concentrate ration consisting of maize only, Group I, and the veld sheep, Group V, experienced longer delay in the onset of the sexuol season than did Groups II, III, and IV.

Previous reference has been made to the range of variation which exists in all groups with regard to the number of dioestrous cycles experienced and the duration of the sexual season. Group III, receiving peanut meal as a supplement, experienced most dioestrous cycles, 12·8, and the mean duration of the sexual season is longest, 229·6 days, the latter being 26 and 20·1 days longer than those of Groups II and IV respectively. The equivalent data of the veld sheep, Group V, do not differ greatly from that of Group IV.

While Group I experienced an average of 11·2 dioestrous cycles, the duration of the sexual season was only 186·1 days, or 15·7 days less than that of the veld sheep and 43·5 days less than that of the group in which the sexual season was of longest duration. The last columns reveal that increased duration of the sexual season of Group III must be attributed to the extension of the latter part of the season. It is apparent that a similar extension in the case of Group V was responsible for the comparatively long season of this group for, as previously stated, the onset of the season was delayed. In this latter respect, the seasons of Groups I and V may be compared. The shorter season of the former group is due to the termination of the sexual season at an average period of 107·3 days before the end of the observation period. It is well to remark at this point that the winter conditions during 1935 were particularly severe, and that, during the latter part of winter, low and high temperatures were experienced while spring rains were exceptionally late. It can only be suggested that the periodic grazing on green cereals of sheep in satisfactory winter condition, results in comparatively favourable sexual activity, as reflected in the number of dioestrous cycles experienced and the extension of the sexual season. In the case of Groups II and IV, the average duration of the inactive period following the sexual season is 16·6 and 26·2 days longer than that of Group III.

The data relative to the periodicity of oestrus in Table II of the text have been analysed and presented in Table IV. It is seen that oestrus recurred with greatest regularity in Group I, the range of the duration of the dioestrous cycles is narrowest, and, in as great a number as 95·1 per cent. of cases, oestrus recurred after 16 to 19 days. The latter percentages in the cases of Groups II, III, and IV reveal insignificant differences between these three groups. The equivalent result in Group V, 77·3 per cent., is considerably below that of the other groups. Dioestrous cycles, the duration of which are multiples of that of the normal cycle, cannot be said to occur during the first or last part of the sexual season; the distribution of such abnormal cycles is very general and there appears to be no relationship between their occurence and the extent of sexual activity during the sexual season (Appendix 1B, Tables VI to X).

TABLE IV.

The Periodicity of Oestrus.

Group.	Total No. of inter-oestrous periods.	Range of periods after which oestrus recurred	Percentage of cases in which oestrus recurred after a period of 16–19 days.
		days.	Per cent.
I................	102	16–49	95·1
II................	103	10–70	82·5
III................	118	14–70	83·0
IV................	92	13–168	81·3
V................	97	14–52	77·3

No explanation can be given for the failure of oestrus to recur with greater consistency; nor is it possible to attribute the significant differences of the irregularity between groups to a specific factor or set of factors. Grant (1934) has pointed out that, when oestrus observations are made only once daily, failure to observe oestrous periods of short duration may result. From the results of Experiment 3 of this thesis, it would appear unlikely that a large percentage of oestrous periods would not be detected by testing for oestrus at 24-hour intervals.

Previous mention has been made of the presence of sheep in all groups, the number of dioestrous cycles of which is considerably less than that of other members of the groups. By examining the data, it is found that in several cases the least active sheep are the lightest sheep in their groups. However, the relationship does not hold good for all cases. Table V of the text has been constructed from Appendix 1B, Tables I to X in order to present this aspect. As the groups were subjected to different treatments for approximately 12 months, the average initial weight of all groups is best used as a basis for classifying the light and heavy weight members of each group. It is seen that, in the cases of Groups I, II, and IV, the mean number of dioestrous cycles experienced by the lighter sheep is 4·4, 3·0, and 4·0 less respectively than that of the heavier sheep; in Groups III and V the equivalent differences are only 1·7 and 1·5 respectively. Also, it becomes obvious that the mean numbers of dioestrous cycles experienced by the lighter sheep are less than the averages for the particular groups. However, attention is drawn to the fact, as indicated by the range of variation of the number of dioestrous cycles, that in all groups individuals of light body weight experienced larger numbers of cycles than the mean value of the particular group.

TABLE V.

Relation between Body Weight and Sexual Activity.

Group.	No. of sheep above (*a*) and below (*b*) average initial weight of 63·5 lb.	No. of dioestrous cycles.		Average No. of dioestrous cycles of the groups.
		Range.	Average.	
I (*a*)................	5	10–18	13·4	11·2
(*b*)................	5	2–14	9·0	
II (*a*)................	6	2–19	12·5	11·3
(*b*)................	4	6–15	9·5	
III (*a*)................	6	10–16	13·5	12·8
(*b*)................	4	3–18	11·8	
IV (*a*)................	6	5–17	11·8	10·2
(*b*)................	4	3–13	7·8	
V (*a*)................	6	7–17	11·3	10·7
(*b*)................	4	4–13	9·8	..

Attention is once more drawn to the fact that the licks of the sheep in this experiment consisted only of salt, bone meal being excluded. The salt consumption varied from 0·19 to 0·25 ounces per sheep per day. However, although the mineral content of the rations of the different groups varied, each content of the rations containing nitrogenous supplements was appreciable, especially in the case in which cotton seed meal was fed (Group II). The analyses of the feed-stuffs used are given in Appendix 1A, Table XXVI.

Special reference is made to the results of sexual activity obtained when cotton seed meal was fed in a low level ration (Experiment 1A, Group III). In this case, reduced sexual activity was observed within the first 12 months of treatment and, during the second sexual season, activity was reduced to a very great extent. In this experiment, 1B, Group II, no detrimental effects are evidenced during the first 12 months as a result of the inclusion of cottonseed meal in a high level ration.

Conclusions.

1. The effects upon the sexual activity of Merino ewes of three nitrogenous concentrates fed as supplements in high level rations were studied over a period of 12 months. The results of such treatments have been compared to that in which no nitrogenous supplement was included, and to that of sheep maintained on veld with good range management. The effects of all treatments upon body weight and wool production have been analysed.

2. With respect to body weight gains, cottonseed meal, peanut meal, and blood meal are suitable supplements to maize and teff hay, as such rations induce greater increase in weight than does a ration consisting of maize as the sole concentrate, or does natural pasture which is supplemented according to general range management.

3. The inclusion of cottonseed meal and blood meal in the ration improves wool production; the addition of peanut meal gives similar results, as does good range management; and the feeding of maize and teff hay without a nitrogenous supplement results in reduced wool yields.

4. Sheep subjected to high planes of nutrition, including adequate quantities of nitrogenous supplements, experience restricted annual sexual activity, although the additions of the supplements lengthen the duration of the sexual season.

   (*a*) Sheep under good range management experience 10·7 dioestrous cycles during a sexual season of 201·8 days' duration.

   (*b*) Sheep on a ration of maize and teff hay experience 11·2 dioestrous cycles during a sexual season of 186·1 days' duration.

   (*c*) Sheep on a ration of maize and teff hay, supplemented by cottonseed meal, experience 11·3 dioestrous cycles during a sexual season of 203·6 days' duration.

(*d*) Sheep on a ration of maize and teff hay, supplemented by peanut meal, experience 12·8 dioestrous cycles during a sexual season of 229·6 days' duration.

(*e*) Sheep on a ration of maize and teff hay, supplemented by blood meal, experience 10·2 dioestrous cycles during a sexual season of 209·5 days' duration.

5. The duration of the sexual season and the number of dioestrous cycles of sheep receiving adequate quantities of nitrogenous supplements, are as variable as in the case of sheep on a highly carbonaceous ration or of sheep which are given good range management.

6. The sexual activity of sheep which are in poor condition, as reflected by body weight, is less than that of sheep which are well conditioned. This fact is largely responsible for the great individual difference with respect to degree of sexual activity.

When a limited number of dioestrous cycles is experienced by individuals, such cycles occur either at the beginning or about the middle of the sexual season.

7. The failure of oestrus to recur with regular periodicity occurs during all stages of the sexual season, and " silent " oestrous periods are experienced by the most active as well as by the least active sheep.

No explanation can be offered for the occasional absence of oestrus and for the significant differences of such absence which is apparent in groups of sheep subjected to various treatments.

EXPERIMENT 1A.

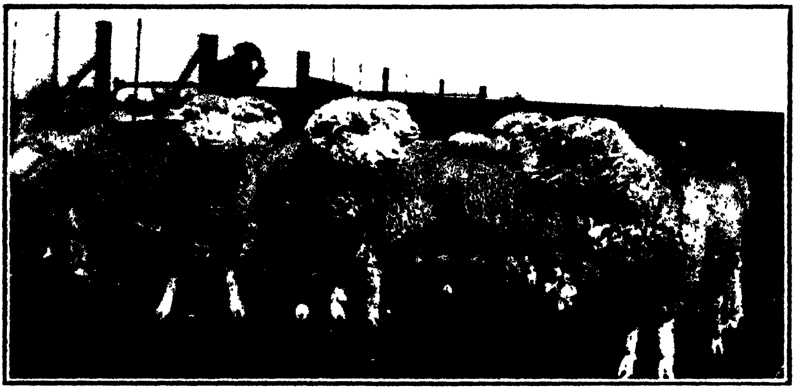


Fig. 1.—Group I: 22.9.33.

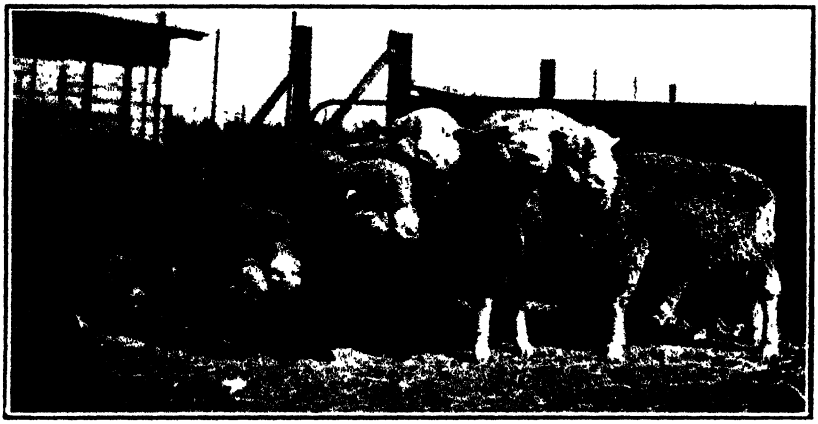


Fig. 2.—Group I: 31.8.34.

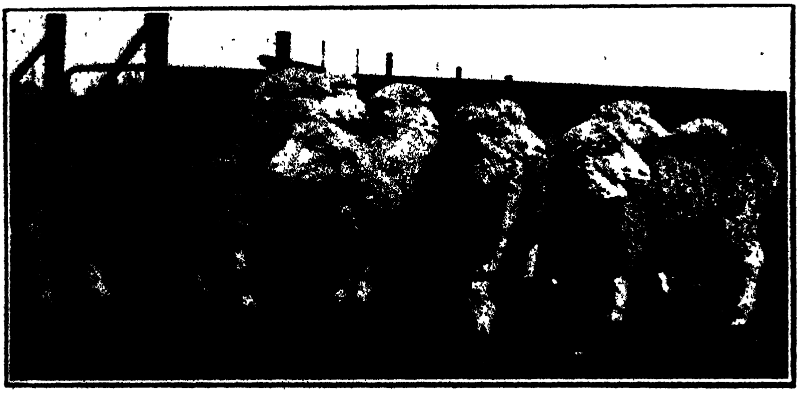


Fig. 3.—Group II: 22.9.33.

EXPERIMENT 1A.

Fig. 4.—Group II: 31.8.34.

Fig. 5.—Group III: 22.9.33.

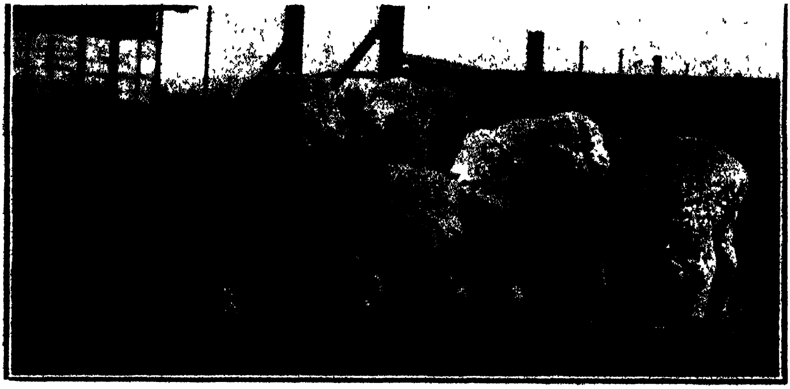


Fig. 6.—Group III: 31.8.34.

EXPERIMENT 1A.

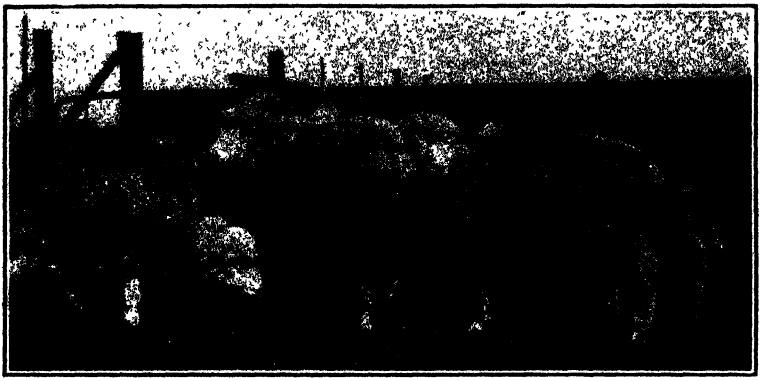


Fig. 7.—Group IV: 22.9.33.

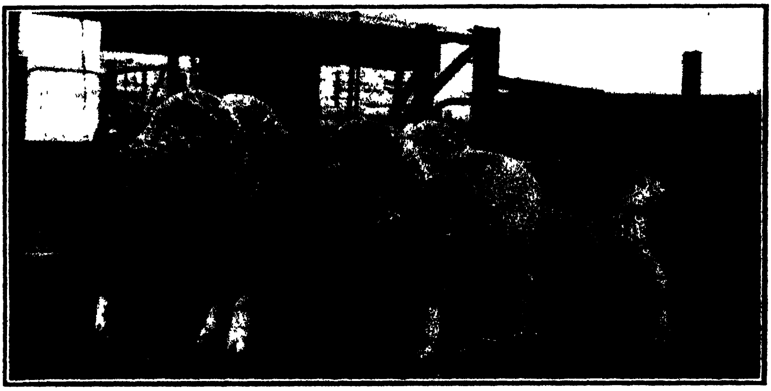


Fig. 8.—Group IV: 31.8.34.

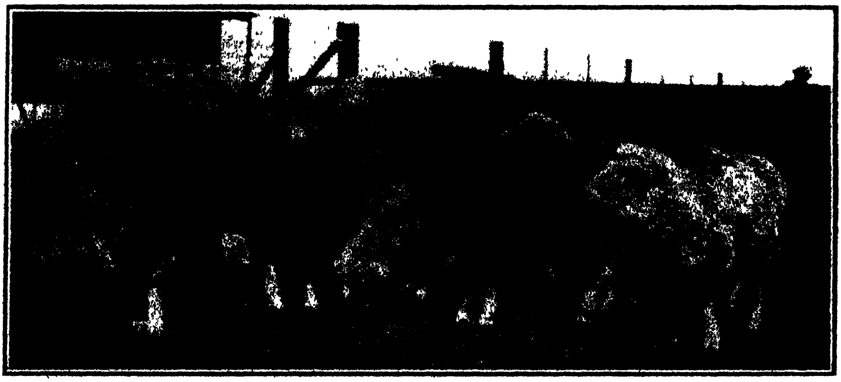


Fig. 9.—Group V: 22.9.33.

EXPERIMENT 1A.

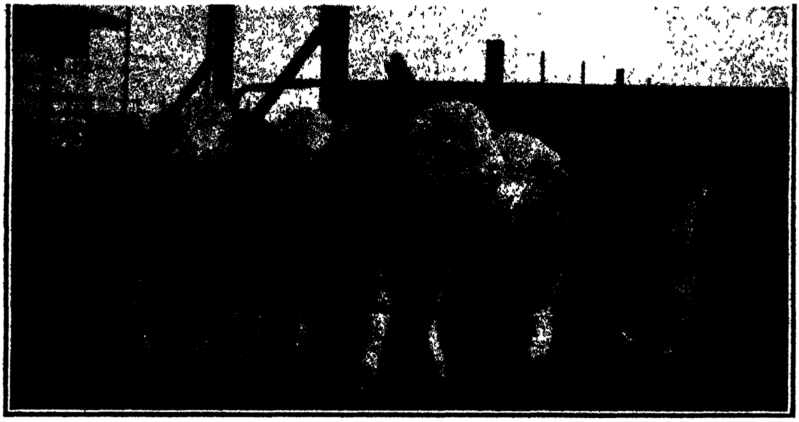


Fig. 10.—Group V: 31.8.34.

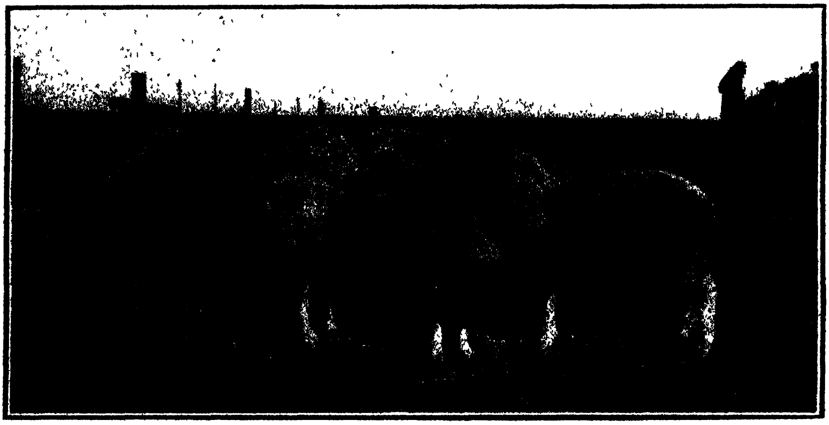


Fig. 11.—Group VI: 22.9.33.

Fig. 12.—Group VI: 31.8.34.

EXPERIMENT 1A.

Fig. 13.—Group VII: 22.9.33.

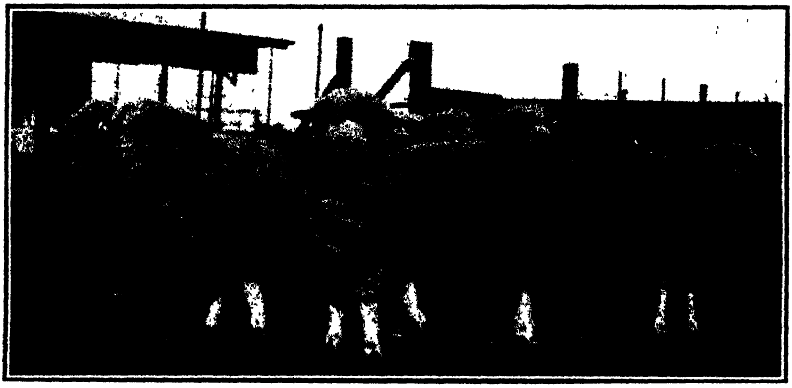


Fig. 14.—Group VII: 31.8.34.

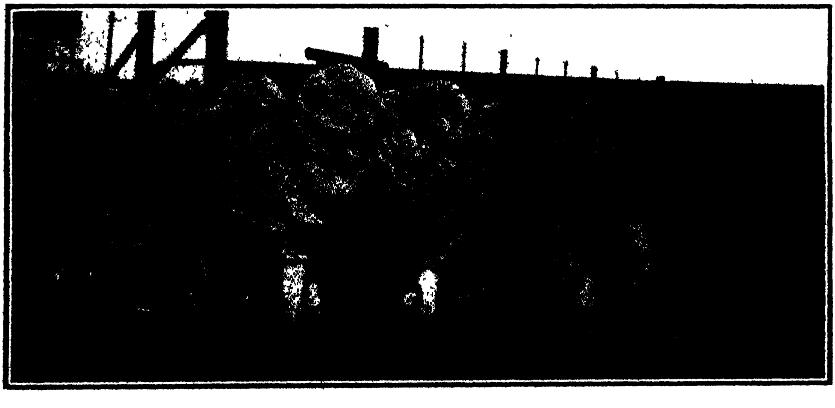


Fig. 15.—Group VIII: 22.9.33.

EXPERIMENT 1A.

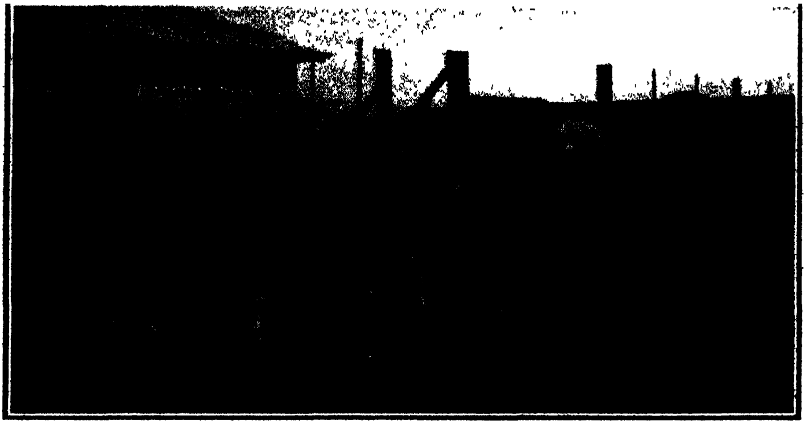


Fig. 16.--Group VIII: 31.8.34.

EXPERIMENT 1B.

Fig. 17.—Group I: 23.7.35.

Fig. 18.—Group II: 23.7.35.

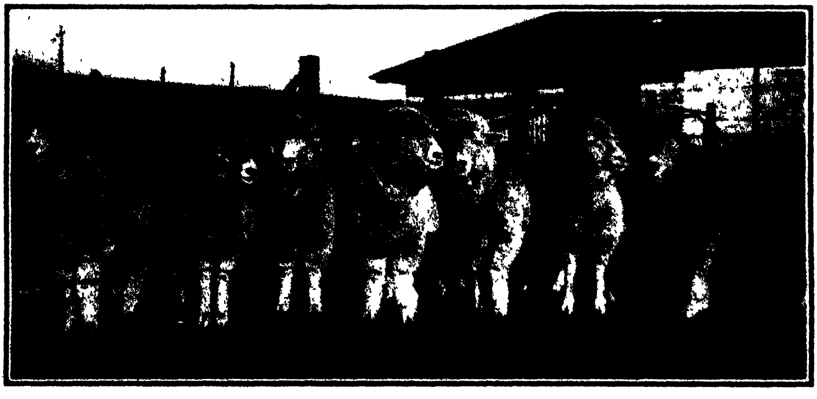


Fig. 19.—Group III: 23.7.35.

EXPERIMENT 1B.

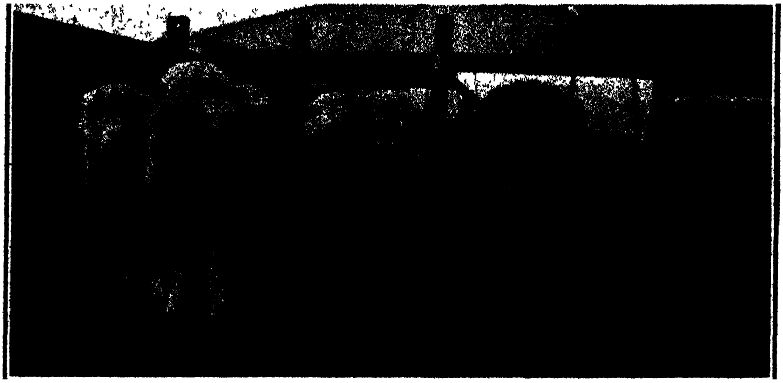


Fig 20.—Group IV: 23.7.35.

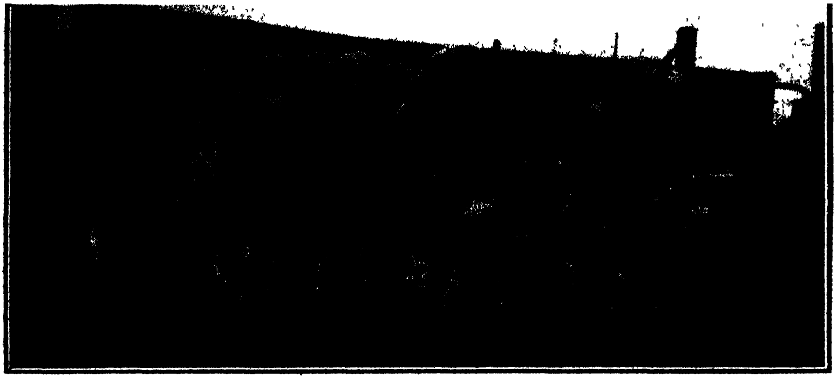


Fig. 21.—Group V: 23.7.35.

EXPERIMENT 2.

THE MORPHOLOGY OF THE OVARIES OF MERINO SHEEP DURING ANOESTRUM.

The object was to study the morphology of the ovaries of Merino sheep during anoestrum.

Materials and Methods.—Sixty-nine Merino flock sheep were slaughtered for macroscopical examination of the ovaries.

The sheep utilized constituted a number of groups which had been under observation in experiments relevant to the present study. Details of the treatments to which the various groups were subjected and their reactions, especially the history of their sexual activity, may be found by consulting Experiment 1A of this thesis. However, brief extracts have been made for incorporation with the data of this experiment in order to facilitate the necessary association between the experiments. In Groups I to VIII of this experiment, the same order of individuals and groups has been maintained as that occurring in Experiment 1A.

All sheep slaughtered had not shown oestrus for a period equivalent to at least two dioestrous cycles of normal duration; the majority of sheep were slaughtered 3 to 4 months after their last exhibition of oestrus; in some exceptional cases no sexual season had occurred and oestrus had not been observed for over a year. Due to existing circumstances, not more than four sheep could be slaughtered weekly, so that a more definite system of slaughtering individuals from each of the groups at specific intervals during anoestrum was not possible. When selecting sheep for slaughter on a particular date, it was attempted to obtain cases the inactive periods of which were, as nearly as possible, multiples of a normal dioestrous cycle.

The sheep were starved for 12 to 14 hours, at the end of which period they were weighed and slaughtered. Immediately after slaughtering, the uteri and ovaries were removed by dissecting along the margins of these organs. The ovaries were placed in small specimen dishes on moist blotting paper on which details for identification had been noted. The uteri were placed in large specimen dishes on moist blotting paper on which the numbers of the ewes were recorded. The specimen dishes were covered until the weighing and measuring of the organs were undertaken and this was completed within an hour after slaughtering.

The procedure of examining the uteri and ovaries was as follows: The uteri were weighed and they were then placed in specimen bottles containing Jore's solution, and on which particulars of identification were noted. The ovaries were weighed and returned to the specimen dishes. The macroscopical examination of individual ovaries was undertaken. Measurements were made as follows: (1) length from pole to pole, (2) depth from the attached to the free border, and

(3) width from the median to the lateral face. Three readings were taken of each dimension and the average of the three readings was recorded. The surface of the ovary was carefully examined and described with respect to the number and size of Graafiian follicles present, the presence or absence and size of corpora lutea, and remnants of previous corpora lutea. The ovary was sectioned along its length from pole to pole, care being taken to observe the presence and the nature of fluid liberated. When follicles and corpora lutea were sectioned, detailed descriptions of these were made. The sectioned ovary was held up to the light in order to obtain a second count of the Graafian follicles and to ascertain whether any small corpora lutea had remained hidden below the surface of the ovary. In cases in which the section through the length of the ovary was not sufficient to expose objects of interest, further sections were made. Directly after the examination of an ovary was completed, it was placed in a specimen jar containing Jore's solution and on which particulars of identification were noted.

The uteri and ovaries were forwarded to the Director of Veterinary Services, Onderstepoort, Pretoria. The histological examinations of these specimens will be reported upon as a separate study.

Results.

As previously indicated, the sheep used in this experiment were obtained from other experiments reported upon in this thesis; hence Groups I to VIII correspond in identical order to Groups I to VIII of Experiment 1A. In order to facilitate reference to the treatment of the groups, Table I of the text is presented in conjunction with the results of this experiment.

TABLE I.

The Treatment of the Groups.

Group.	Oestrous observations commenced.	Treatment (rations per sheep per day).	No. of sheep slaughtered.
I	24. 7.32	Dry-lot: Maize, 4 oz.; teff hay, 2·5 ℔.; bonemeal and salt ad lib	9
II	24. 7.32	„ Maize, 4 oz.: teff hay, 2 5 ℔.; salt ad lib	10
III	24. 7.32	„ Maize, 2·7 oz.; cotton seed meal, 1·3 oz; teff hay, 2·5 ℔.; salt ad lib...	9
IV (*a*)	24. 7.32	„ Maize, 4 oz; teff hay, 2·5 ℔.; bonemeal and salt ad lib	—
(*b*)	2. 3.33	„ Teff hay, 3 ℔.; bonemeal and salt ad lib	9
V	24. 7.32	„ Maize, 4 oz.; teff hay, 3·0 ℔.; bonemeal and salt ad lib	7
VI	7.10.32	Pasture: Bonemeal and salt ad lib	9
VII	7.10.32	„ Maize, 8–12 oz.; bonemeal and salt ad lib	7
VIII	1. 5.33	„ Bonemeal and salt, green grazing during winter	9

NOTE.—Although the above Groups I to VIII each contained 10 sheep at the commencement of the observations, in certain instances individuals died during the period of the experiments, and in other instances oestrus occurred after relatively short anoestrus periods.

The detailed results of this experiment are given in Appendix 2. Complete details of the results of the macroscopical examinations of the ovaries are outlined, while, in each case, brief sexual histories, extracted from Experiment 1A, have been appended (Experiment 1A, Appendix 1, Tables IX to XXIV).

The data recorded in Appendix 2 have been compiled in Tables II to X of the text in order to reflect the results of the examinations of the ovaries more clearly. It must be understood that the counts of the number of Graafian follicles present were obtained without the use of magnification.

Discussion.

The British breeds of sheep experience an anoestrous period in their home country and abroad during the spring and summer months (Heape, 1901; Marshall, 1903, 1922; Marshall and Hammond, 1926; Roberts, 1921; Cole and Miller, 1933; Grant, 1934). Although Quinlan and Maré (1931) found that Merino sheep under South African Karroo conditions experience a continuous series of dioestrous cycles throughout the year, Küpfer (1928) observed that, in the western Free State, South Africa, Merino and Woolled Persion sheep enter a sexually inactive period during the late winter months.

The oestrous observations carried out on the sheep slaughtered for this experiment, indicate that the sheep had experienced definite periods of seasonal sexual activity and inactivity. The sexual seasons of the sheep have been discussed in the report of Experiment 1A. It has been indicated in a previous section of the report of this experiment that all sheep were in anoestrum at the time of slaughter.

No previous records upon the weights of the uteri of sheep are available.

The weights and measurements of the ovaries of Merino sheep during the ovarian cycle are given by Quinlan and Maré (1931), who found that "... the ovaries are lightest just subsequent to ovulation and heaviest when the corpus luteum (1) reaches its maximum development, that is, from the sixth day of the interoestrous period". These investigators found that the lightest ovaries weighed 0·67 and 0·63 gms.; the heaviest weighed 2·25 gms. on the 10th day of the interoestrous period; and an ovary containing a corpus luteum measuring 1·2 × 1·0 cm. on the 13th day of the interoestrous period, weighed 1·98 gms. Further, it is indicated that the size of the ovary is greatly affected by the size of the corpus luteum and to a smaller extent by the size of Graafian follicles. It is stated with regard to the latter, that rapid follicular development occurs during the first few days after ovulation, when follicles measuring 0·75 to 0·86 cm. may be found. Grant's (1934) observations on Scottish sheep led to the conclusion that follicular development during the earlier part of the interoestrous period is less rapid. It appears from the data of the former authors that mature follicles in the ovaries of Merino sheep measure about 0·8 to 1·0 cm.

TABLE II.

Group I.—Macroscopic Examination of the Ovaries.

Sheep No.	Age.	Condition.	Weight	Last oestrus observed	Period between last oestrus observed and slaughter.	Uterus weight.	Ovaries.				*Graafian Follicles.*			*Corpora Lutea.*	
							Left.		Right.		No. observed.		Largest.		
							Weight.	Size.	Weight	Size.	Left. ovary.	Right. ovary.		I.	II.
	years.		lb.	date.	days.	gm.	gm.	cm.	gm.	cm.			cm.	cm.	cm.
29252	4	good	74·0	2.8.34	91	22·5	0·82	1·3×1·3×0·9	0·63	1·2×1·1×0·8	9	6	0·6	0	0
29270	4	fair	61·0	22.7.33	399	—	0·70	1·2×1·0×0·8	0·56	1·1×1·0×0·7	6	8	0·5	0	0
29324	—	—	—	—	not slaughtered	—	—	—	—	—	—	—	—	—	—
29325	4	fair	62·5	7.8.34	150	20·5	0·62	1·5×1·2×0·7	0·63	1·2×1·1×0·9	11	3	0·3	0	0
29328	4	poor	58·5	19.5.34	111	26·5	0·58	1·1×1·1×0·7	0·66	1·1×1·1×0·8	3	5	0·5	0	0
29340	4	good	80·5	22.4.34	138	22·5	0·56	1·3×1·0×0·8	0·72	1·3×1·1×0·8	15	15	0·3	0	0
29805	4	good	65·0	10.8.34	142	30·5	0·55	1·2×1·1×0·8	0·65	1·3×1·1×0·8	11	8	0·6	0	0
29815	4	poor	48·0	16.6.34	98	15·5	0·51	1·2×1·0×0·8	0·38	1·2×0·8×0·6	8	7	0·3	0	0
32476	3½	fair	60·0	26.6.34	88	21·5	0·54	1·4×1·0×0·7	0·40	1·3×0·8×0·6	11	3	0·3	0	0
32491	3½	fair	64·5	3.8.34	154	21·0	0·50	1·4×0·9×0·7	0·46	1·3×0·95×0·75	4	3	0·5	0	0

TABLE III.

Group II.

35508	4	good	67·0	1.8.34	92	25·5	0·78	1·4×1·3×0·8	0·66	1·4×1·1×0·6	12	12	0·5	0·5× 0·5	0
35509	4	good	74·0	9.7.34	95	18·5	0·68	1·2×1·2×0·8	0·51	1·2×1·0×0·7	5	4	0·3	0	0
29274	4	good	67·0	10.7.34	94	24·0	0·49	1·2×1·0×0·7	0·63	1·4×1·0×0·8	7	1	0·6	0	0
29279	4	fair	63·0	14.5.33	458	—	0·39	0·9×0·8×0·6	0·42	1·0×0·9×0·6	6	5	0·4	0	0
29335	4	poor	44·0	31.7.34	143	15·5	0·59	1·4×1·0×0·8	0·74	1·3×1·2×0·85	7	6	0·4	0	0
29341	4	fair	67·0	17.7.34	164	40·0	0·71	1·4×1·3×0·8	0·66	1·3×1·1×0·8	9	15	0·2	0·5× 0·4	0
29793	4	fair	56·5	26.7.34	155	36·5	1·40	1·5×1·2×1·6	0·58	1·3×1·05×0·7	7	10	0·5	1·2× 1·0	0
29827	4	good	73·0	12.8.34	138	24·0	0·64	1·2×1·2×0·7	0·63	1·1×1·1×0·8	10	14	0·4	0·4× 0·4	0
32480	4	fair	61·0	28.7.34	146	27·5	0·62	1·1×0·9×0·75	0·48	1·2×0·9×0·7	11	8	0·5	0·2× 0·2	0
32493	3½	good	74·0	15.8.34	128	21·0	0·54	1·0×1·2×0·7	0·46	1·2×1·0×0·65	2	5	0·5	0	0

TABLE IV.

Group III.—Macroscopic Examination of the Ovaries.

Sheep No.	Age	Condition.	Weight	Last oestrus observed	Period between last oestrus observed and slaughter.	Uterus weight.	Ovaries. Left. Weight.	Ovaries. Left. Size.	Ovaries. Right. Weight	Ovaries. Right. Size.	Graafian Follicles. No. observed. Left ovary.	Graafian Follicles. No. observed. Right ovary.	Graafian Follicles. Largest.	Corpora Lutea. I.	Corpora Lutea. II.
	years.		lb.	date.	days.	gm.	gm.	cm.	gm.	cm.			cm.	cm.	cm.
35499	4	fair	68·5	11.5.34	119	20·5	0·89	1·6×1·1×0·9	0·88	1·5×1·1×0·7	6	4	0·2	0	0
35498	4	fair	57·0	14.7.33	405	18·5	0·61	1·2×1·1×0·7	0·42	1·0×0·9×0·6	10	6	0·3	0·2× 0·2	0
29258	4	good	89·0	19.7.34	105	23·5	0·72	1·4×1·2×0·7	0·80	1·4×1·2×1·0	7	7	0·5	0	0
29265	4	fair	63·0	28.6.34	106	27·5	0·67	1·2×1·1×0·7	0·57	1·2×0·9×0·8	4	6	0·5	0	0
29273	4	poor	65·0	27.5.34	110	22·5	0·68	1·3×1·1×0·9	0·55	1·2×1·1×0·8	6	6	0·6	0	0
29283	4	good	73·0	30.3.34	151	19·5	0·45	1·2×1·1×0·7	0·52	1·2×1·1×0·8	5	6	0·4	0·2× 0·4	0
29330	died 22.11.32	—	—	—	—	—	—	—	—	—	—	—	—	—	—
29334	4	fair	58·0	19.6.34	95	18·5	0·52	1·2×1·0×0·8	0·38	1·1×0·9×0·8	7	7	0·3	0	0
32482	3½	fair	65·0	9.7.34	115	18·5	0·63	1·5×1·0×0·7	0·48	1·4×0·9×0·6	10	4	0·3	0	0
32495	3½	good	88·0	31.8.34	57	20·5	0·48	1·4×1·0×0·6	0·58	1·4×1·1×0·7	3	2	0·5	0	0

TABLE V.

Group IV.

29261	4	poor	52·0	7.2.34	204	19·5	0·56	1·2×1·1×0·7	0·53	1·3×0·9×0·7	8	5	0·3	0	0
29268	4	fair	64·0	30.7.34	66	21·5	0·67	1·5×1·1×0·8	0·50	1·3×1·1×0·7	10	7	0·3	0	0
29298	4	fair	69·0	26.6.34	100	23·5	0·44	1·3×1·0×0·7	0·72	1·5×1·1×0·8	8	10	0·2	0	0
29306	4	fair	64·5	1.7.34	95	19·5	0·60	1·3×1·2×0·8	0·75	1·5×1·1×0·8	6	9	0·2	0	0
29309	4	fair	62·5	20.6.34	99	15·5	0·62	1·5×1·0×0·8	0·88	1·6×1·2×0·9	10	19	0·2	0	0
29316	4	fair	69·0	16.6.34	98	24·0	0·58	1·4×1·0×0·7	0·60	1·5×1·1×0·7	6	6	0·4	0	0
29822	4	poor	50·0	20.7.33	406	16·0	0·53	1·2×0·9×0·7	0·53	1·1×1·0×0·7	9	7	0·3	0	0
29825	4	fair	59·5	19.5.34	118	18·5	0·46	1·2×1·0×0·7	0·64	1·3×1·1×0·7	4	10	0·2	0	0
29830	died 16.1.34	—	—	—	—	—	—	—	—	—	—	—	—	—	—
35500	4	fair	66·0	11.9.33	353	17·5	0·45	1·1×0·9×0·6	0·61	1·2×1·0×0·7	6	7	0·5	0	0

TABLE VI.

Group V.—Macroscopic Examination of the Ovaries.

Sheep No.	Age.	Condition.	Weight	Last oestrus observed	Period between last oestrus observed and slaughter.	Uterus weight.	Ovaries.				*Graafian Follicles.*			*Corpora Lutea.*	
							Left.		Right.		No. observed.		Largest.	I.	II.
							Weight.	Size.	Weight	Size.	Left ovary.	Right ovary.			
	years.		lb.	date.	days.	gm.	gm.	cm.	gm.	cm.			cm.	cm.	cm.
35507	aged	fair	51·0	6.9.33	351	32·0	0·64	1·4×1·1×0·6	0·53	—	4	4	0·3	0	0
35506	6	fair	61·0	27.8.34	109	40·0	1·13	1·8×1·4×0·8	1·22	1·8×1·5×0·9	12	12	0·4	0	0
35505	died 13.12.33	—	—	—	—	—	—	—	—	—	—	—	—	—	—
13367	died 27.12.33	—	—	—	—	—	—	—	—	—	—	—	—	—	—
15329	6–7	good	74·0	8.7.33	413	50·5	0·66	1·5×1·0×0·6	0·80	1·4×1·2×0·8	2	5	0·5	L: 0.2×0·3 R: 0.2×0·2	0
21658	6	good	81·0	16.10.34	52	34·5	0·90	1·6×1·2×0·7	0·93	1·6×1·2×0·9	12	7	0·5	0	0
25876	6	fair	58·0	11.7.34	156	27·0	0·65	1·5×1·1×0·75	0·85	1·5×1·3×0·8	14	15	0·2	0	0
25882	died 24.2.33	—	—	—	—	—	—	—	—	—	—	—	—	—	—
25883	6	poor	53·0	13.6.34	101	32·5	0·58	1·3×1·1×0·7	0·60	1·3×1·1×0·8	12	6	0·3	0	0
25907	7	poor	53·0	9.10.34	52	34·5	0·51	1·1×1·2×0·6	0·42	0·9×1·1×0·6	3	4	0·5	0	0

TABLE VII.

Group VI.

15257	6	fair	75·0	10.8.34	91	48·0	1·66	2·2×1·4×0·9	0·69	1·5×1·2×0·8	7	8	0·4	1·1×1·2	0
15327	7	fair	63·5	5.8.34	159	60·5	1·93	1·8×1·9×1·1	1·03	1·5×1·5×0·7	6	15	0·4	1·1×1·2	0
21504	7	poor	57·0	23.8.34	141	35·5	0·75	1·5×1·1×0·8	0·48	1·1×1·1×0·7	10	11	0·5	0·6×0·6	0
21607	died 30.9.33	—	—	—	—	—	—	—	—	—	—	—	—	—	—
24928	7	fair	72·0	25.9.34	68	45·0	1·35	1·9×1·4×0·9	1·20	1·8×1·4×0·8	5	11	0·3	0	0
25873	6	good	80·0	27.7.34	168	41·5	0·79	1·5×1·3×0·8	1·15	1·6×1·5×0·9	7	15	0·3	0·3×0·3	0
35501	7	v. gd.	84·0	4.9.34	101	37·5	0·81	1·5×1·5×0·9	0·48	1·4×0·9×0·6	5	3	0·55	0·6×0·5	0
35496	7	v. gd.	87·0	3.9.34	88	20·5	0·56	1·3×1·0×0·7	0·61	1·4×1·0×0·7	4	6	0·5	0	0
35502	6	poor	68·0	27.6.34	198	33·5	0·93	1·4×1·3×1·0	0·72	1·3×1·1×0·8	24	7	0·5	0	0
35497	7	good	95·0	3.9.34	88	29·5	0·65	1·5×1·1×0·7	0·68	1·2×1·2×0·9	8	4	0·6	0	0

TABLE VIII.

Group VII.—Macroscopic Examination of the Ovaries.

Sheep No.	Age.	Condition.	Weight	Last oestrus observed	Period between last oestrus observed and slaughter.	Uterus weight.	Ovaries.				Graafian Follicles.			Corpora Lutea.	
							Left.		Right.		No. observed.		Largest.		
							Weight.	Size.	Weight	Size.	Left. ovary.	Right. ovary.		I.	II.
	years.		lb.	date.	days.	gm.	gm.	cm.	gm.	cm.			cm.	cm.	cm.
15351	7	good	84·0	29.10.34	33	52·5	0·72	1·3×1·2×0·9	0·60	1·4×1·0×0·7	6	2	0·8 (mature)	0	0
15521	—	—	—	—	not slaughtered	—	—	—	—	—	—	—	—	—	—
22210	6	good	75·0	11.9.34	66	31·5	1·20	1·4×1·5×0·9	1·10	1·5×1·2×0·7	20	15	0·3	0	0
22547	—	—	—	—	not slaughtered	—	—	—	—	—	—	—	—	—	—
24955	—	—	—	—	not slaughtered	—	—	—	—	—	—	—	—	—	—
25105	6	v. gd.	95·0	19.9.34	79	30·5	0·82	1·5×1·2×0·8	1·79	1·9×1·4×1·2	17	19	0·5	1·5×1·55	0
25908	7	good	83·5	2.9.34	103	47·5	1·37	1·4×1·8×1·25	0·86	1·45×1·2×0·9	4	6	0·4	1·2×0·8	0·15×0·15
25938	7	good	72·0	15.5.34	121	77·5	1·52	1·7×1·6×1·1	1·22	1·6×1·6×0·9	5	6	0·5	0·2×0·2	0
35503	6	v. gd.	99·0	24.8.34	90	47·5	0·60	1·3×1·0×0·8	2·63	1·9×1·4×1·7	4	2	0·7	1·0×1·2	0·3×0·5
35504	6	v. gd.	98·0	15.9.34	55	49·5	1·14	1·6×1·2×0·9	0·91	1·4×1·3×0·9	15	6	0·6	0·8×0·5	0

TABLE IX.

Group VIII.

Sheep No.	Age.	Condition.	Weight	Last oestrus observed	Period between last oestrus observed and slaughter.	Uterus weight.	Left ovary Weight.	Left ovary Size.	Right ovary Weight	Right ovary Size.	Graafian Follicles No. observed Left ovary.	Right ovary.	Largest.	Corpora Lutea I.	II.
21500	6	v. gd.	84·0	2.10.34	38	45·5	0·87	1·6×1·1×0·8	1·53	1·4×1·2×1·4	12	9	0·8	1·2×1·0	0
22059	6	v. gd.	87·0	4.9.34	101	39·5	0·72	1·2×1·0×0·8	1·13	1·4×1·5×1·0	11	4	0·4	1·2×0·9	0
25025	6	v. gd.	97·0	11.7.34	164	47·5	1·35	1·7×1·5×1·0	1·16	1·7×1·6×0·9	14	10	0·6	0·7×0·6	0
25948	—	—	—	—	not slaughtered	—	—	—	—	—	—	—	—	—	—
35708	7	v. gd.	83·0	5.8.34	78	40·0	0·97	1·6×1·2×0·8	1·05	1·5×1·2×0·9	9	15	0·5	0	0
35732	6	good	74·0	24.7.34	115	30·5	0·60	1·4×1·0×0·8	0·71	1·3×1·2×0·8	7	8	0·3	0	0
35994	6	v. gd.	100·0	18.9.34	80	37·0	0·84	1·4×1·3×0·8	0·89	1·5×1·2×0·9	12	9	0·6	0	0
37058	7	good	83·0	9.9.34	117	56·5	0·75	1·5×1·05×0·8	0·74	1·5×1·1×0·8	5	4	0·4	0·5×0·3	0
37059	6	v. gd.	89·0	30.9.34	40	51·5	0·99	1·5×1·4×1·0	0·61	1·4×1·0×0·8	4	6	0·7	0·5×0·5	0
37061	6	v. gd.	102·0	18.9.34	108	47·0	1·41	1·65×1·3×1·1	0·63	1·2×1·15×0·7	10	9	0·4	1·0×0·9	0

In discussing the results of the examination of the ovaries of the sheep in this experiment, it appears best to consider each of the groups separately at first, as the various groups were subjected to different treatments while under observation in Experiment 1A.

Group I.—The group was maintained on a low level ration of maize, teff hay, bonemeal and salt (Table I).

The results of the macroscopic examinations of the ovaries are given in Table II of the text; the weights of the uteri have been included.

No marked relationship exists between body weight or condition and the weight of the uterus, although the uterus of the lightest and a poor conditioned sheep, No. 29851, weighed only 15·5 gms. On the other hand, it must be pointed out that the uterus of another sheep in poor condition, sheep No. 29328, weighed 26·5 gms.; however the live weight of this sheep exceeded that of the former sheep by 10·5 lb. It is of interest to note that the periods between the last oestrus observed and the date of slaughter of these sheep were 111 and 98 days respectively.

The majority of the ovaries weigh less than the lightest ovaries observed by Quinlan and Maré (1931) in Merino sheep; the sizes of the former are also somewhat less than those of the latter. Although some of the smallest and lightest ovaries contain only a small number of Graafian follicles, other light ovaries contain even more follicles than the heaviest and the largest. Most follicles are small and, although follicles measuring 0·5 and 0·6 cm. are present, none were considered to be approaching maturity. The poor conditioned sheep had light ovaries, but the two ovaries of each sheep contain between 8 and 15 follicles; in one case the largest follicle measured 0·5 cm.

The fact that no corpus luteum was present in any of the ovaries indicates that ovulation had not occurred recently.

Group II.—The group was maintained on a low level ration of maize, teff hay, and salt (Table I).

The results of the macroscopic examinations of the ovaries are given in Table III of the text; the weights of the uteri have been included.

Considerable variation exists between the weights of the uteri of the sheep in fair and good condition, the range being from 18·5 to 40·0 gms.; however, the sheep in poorest condition (44 lbs.) had a uterus weighing only 15·5 gms.

Fifty per cent. of the ovaries may be considered light in weight and of small dimensions, the remainder more nearly approach those at particular stages described by Quinlan and Maré (1931). It is obvious from the table, that the larger and heavier ovaries are those containing corpora lutea; also, it is apparent that the latter ovaries have more numerous follicles, although they do not all contain comparatively large follicles.

The presence of the corpora lutea indicate that ovulation had occurred recently, although it must be pointed out that in no case is there a second corpus luteum present, indicating that the last ovulation was not preceded by an ovulation. In such instances, ovulation must have occurred without the exhibition of oestrus, as, in such cases, the periods between the last oestrus observed and the date of slaughter ranged between 92 and 164 days.

Group III.—The group was maintained on a low level ration of maize, cotton seed meal, teff hay, and salt (Table I).

The results of the macroscopic examinations of the ovaries are given in Table IV of the text; the weights of the uteri have been included.

The weights of the uteri range between 18·5 and 27·5 gms. and the weight of the uterus of the poorest conditioned sheep exceeds that of the average of the group.

The weights and the dimensions of the ovaries vary considerably; only the largest equal the lightest of those at particular stages described by Quinlan and Maré (1931). One of the heaviest and best conditioned sheep, No. 32495, is seen to have light ovaries containing relatively few Graafian follicles.

In two cases, small corpora lutea are present, so that ovulation had occurred in each case; however, no evidence of a preceding ovulation exists. The ovulations occurred without the exhibition of oestrus and it is to be noted that in one case, Sheep No. 35498, oestrus had not been observed for 405 days.

Group IV.—The group was maintained on a low level ration of teff hay, and salt (Table I).

The results of the macroscopic examinations of the ovaries are given in Table V of the text; the weights of the uteri have been included.

The weights of the uteri do not vary a great deal, the range being 15·5 to 24·0 gms.

In the majority of cases, the ovaries are small and light in weight. While the follicles are small, appreciable numbers are present in most ovaries.

No corpora lutea are present, indicating the absence of recent ovulations. The periods between the last oestrus observed and the date of slaughter, range between 66 and 406 days.

Group V.—The group was maintained on a low level ration of maize, teff hay, bonemeal, and salt (Table I).

The results of the macroscopic examinations of the ovaries are given in Table VI of the text; the weights of the uteri have been included.

There is no relationship between live weight or condition and the weights of the uteri.

The weights and dimensions of the ovaries vary considerably and so do the numbers of follicles present in the ovaries. In three out of seven cases totals of only 7 and 8 follicles are present.

In one case only is a corpus luteum present in each of the ovaries; these corpora are very similar and they no doubt originated at a double ovulation. It is to be noted that oestrus had not been observed in this sheep, No. 15329, for 413 days.

Group VI.—The group was maintained on natural pasture throughout the year supplemented only by a mineral lick (Table 1).

The results of the macroscopical examinations of the ovaries are given in Table VII of the text; the weights of the uteri have been included.

Considerable variation exists between the weights of the uteri, which range between 20·5 and 60·5 gms. Two of the best conditioned sheep have the lightest uteri and oestrus was observed in these sheep only 88 days previous to the date of slaughter.

The variations in the weights and measurements of the ovaries of individuals is appreciable; only in certain instances can this be accounted for by the presence of corpora lutea. The number of follicles in both ovaries ranges from 8 to 31. Follicles of 5 and 6 cm. are present in many of the ovaries, but, in other instances, the largest follicles are smaller in size.

Corpora lutea of varying sizes are present in five out of the nine cases examined, but in no case is a second corpus luteum (c.1.II) present. The corpora lutea are considered to be corpora at various stages during interoestrous periods.

Group VII.—The group was maintained on natural pasture supplemented throughout the year by maize and a mineral lick (Table 1).

The results of the macroscopic examinations are given in Table VIII of the text; the weights of the uteri have been included.

All the sheep were in good and very good condition. The weights of the uteri range from 30·5 to 77·5 gms.; the sheep possessing the heaviest uterus had not shown oestrus for 121 days.

The weights and measurements of the ovaries are seen to be affected by the presence of corpora lutea which are present in five out of the seven cases examined. It is seen that the lightest and smallest ovaries are those of Sheep No. 15351 which had ceased sexual activity only 33 days previous to the date of slaughter. The ovaries of this sheep contain only a total of eight discernible follicles, the largest of which is 0·3 cm. In the case of Sheep No. 15921, slaughtered 66 days after the termination of the sexual season, the ovaries are appreciably heavier and larger; they contain a total of 35 follicles, but the largest is only 0·3 cm. The majority of the cases in which corpora lutea are seen to have been present, contain relatively few follicles.

The corpora lutea are considered to have been in different stages of the interoestrous period and it must be noted that in two cases corpora lutea (II) of the previous interovulation periods are found to be present.

Group VIII.—The group was maintained on natural pasture supplemented by green cereal grazing during the winter months and by a mineral lick throughout the year (Table I).

The results of the macroscopic examinations of the ovaries are given in Table IX; the weight of the uteri have been included.

All the sheep are seen to have been in good and very good condition. The weights of the uteri range from 30·5 to 56·5 gms. There appears to be no important relationship between the condition and weights of the sheep and the weights of the uteri, neither between the weights of the uteri and the lengths of the periods of sexual inactivity.

The variations in the weights of the ovaries are due to the presence or absence of corpora lutea, although the ovaries of the cases in which corpora are not present are not small and light, and they contain appreciable numbers of follicles the largest of which are 0·5 and 0·6 cm. in diameter. The total numbers of follicles in the ovaries containing corpora lutea vary from 9 to 24.

Corpora lutea are present in six out of the nine cases examined; the corpora appear to be in various stages of the interoestrous period. In no case is a corpus luteum of the previous interovulation period present.

A summary of the macroscopic examinations of the ovaries of Groups I to VIII is given in Table X of the text. This table permits a comparison of the groups and it should reflect any significant differences due to the treatments to which the sheep were subjected for extended periods (Table I).

It is seen that the sheep in Groups I to IV were of the same age and that they were somewhat younger than those in the remaining groups. The latter fact may, to some extent, influence the value of the following interpretations, but it must be remarked that sheep of four years old are fully grown and mature.

The weight reaction of the groups to the treatment has been fully discussed in the report of Experiment 1A. However, a few brief remarks here would be of interest. It is seen that the inclusion of bonemeal in the ration of Group I, did not give the favourable reflection that might have been expected, as the condition and weight of the sheep in Group II are somewhat better. The addition of a protein-rich concentrate to the ration and the exclusion of bonemeal, as in Group III, increased the mean weight above that of Groups I and II, although only one-third of the sheep acquired good condition. The exclusion of maize from a ration similar to that of Group I, cannot be said to have had a very marked effect upon the mean weight of Group IV, although the majority of the sheep have been described to have been in only fair condition.

TABLE X.

A Summary of the Macroscopic Examinations of the Ovaries.

Group.	No. of sheep.	Average age.	Frequencies of condition.				Average weight.	Class frequencies of period of days between last exhibition of oestrus and date slaughtered.					Average weight of uterus.	Ovaries.				Graafian follicles.		Corpora Lutea.	
														Left.		Right.					
			Poor.	Fair.	Good.	Very good.		34–68.	69–103.	104–138.	139–173.	174 and over		Average weight.	Average size.	Average weight.	Average size.	Average No. observed in both ovaries.	Largest range.	I No.	II No.
		Yrs.					lb.						gm.	gm.	cm.	gm.	cm.		cm.		
I....	9	3·9	2	4	3	0	62·7	0	3	2	3	1	22·6	0·60	1·3×1·1×0·8	0·56	1·2×1·0×0·8	15·1	0·3–0·6	0	0
II...	10	4·0	1	4	5	0	64·6	0	3	2	4	1	25·8	0·68	1·2×1·1×0·8	0·58	1·2×1·0×0·7	15·6	0·2–0·6	5	0
III..	9	3·9	1	5	3	0	69·6	1	1	5	1	1	21·1	0·63	1·3×1·1×0·7	0·58	1·3×1·0×0·8	11·7	0·2–0·6	2	0
IV...	9	4·0	2	7	0	0	61·8	1	4	1	0	3	19·5	0·55	1·3×1·0×0·7	0·64	1·4×1·1×0·7	16·3	0·2–0·5	0	0
V....	7	6·6	2	3	2	0	61·6	2	1	1	1	2	35·8	0·72	1·4×1·2×0·7	0·76	1·2×1·0×0·7	16·0	0·2–0·5	2	0
VI...	9	6·6	2	3	2	2	75·7	1	4	0	3	1	39·0	0·94	1·6×1·3×0·9	0·78	1·4×1·2×0·8	17·3	0·3–0·6	5	0
VII..	7	6·4	0	0	4	3	86·6	3	3	1	0	0	48·1	1·05	1·5×1·4×1·0	1·30	1·6×1·3×1·0	18·1	0·3–0·8	5	2
VIII.	9	6·2	0	0	2	7	88·8	2	3	3	1	0	43·9	0·94	1·5×1·2×0·9	0·34	1·4×1·2×0·9	17·5	0·4–0·8	6	0

The older sheep in Group V received similar treatment to Group I. It has been indicated in the report of Experiment 1A that the former group maintained a more constant weight than the latter group, which showed a gradual increase almost equivalent to the weight of the growth of wool.

Groups VI, VII, and VIII were maintained on natural pasture. The supplementary feeding of maize in the case of Group VII is reflected to appreciable advantage with respect to condition and weight. However, the condition and mean weight of Group VIII show improvement over that of Group VII; the former group was permitted green grazing throughout the year.

The class frequencies of the period between the termination of the sexual season and the date of slaughter are given in Table X. Each class extends for a period of 34 days or two normal dioestrous cycles. The difficulty of slaughtering large numbers of sheep at one time has been indicated. In cases in which no sexual activity occurred during the last sexual season, or in which the sexual season was abnormally short, the period between the last oestrus observed and the time of slaughter is comparatively long.

The average weights of the uteri have been computed and they are given in the table. The uteri of the younger sheep in Groups I to IV are considerably lighter than those of the older sheep in the remaining groups, but, as the former groups may be considered to have been mature at four years of age, the difference has, no doubt, resulted from the treatment on low level rations for a period of 744 days (Experiment 1A, Table V). It is interesting to note that the mean weight of the uteri of Group II exceeds that of Group I by 3·2 gms.; that of Group I exceeds that of Group III by 1·5 gms. and that of Group IV by 3·1 gms. Sheep in Group IV, which had been on a low level ration consisting only of teff hay, bonemeal, and salt for a period of 520 days, had the lightest uteri ranging from 15·5 to 24·0 gms. and averaging 19·5 gms. In this connection, it is of interest to recall the results reflected in Experiment 1A relative to the number of dioestrous cycles and the duration of the last sexual season of the groups. The section of the table (Experiment 1A, Table VI) is repeated here to permit an easier comparison, and it is referred to as Table XI in this report. It appears from the table that, while little difference in sexual activity exists between Groups I and II, significant differences occur in the cases of Groups III and IV, and especially in the latter group.

The uteri of the older sheep in Group V are 13·2 gms. heavier than those of Group I which received similar treatment, but the sheep in the former group were older when the treatment was commenced. It appears, therefore, that low level rations inhibit the development of the uteri of young sheep.

The weights of the uteri of Group V may be compared with those of Groups VI, VII, and VIII, which were maintained on natural pasture with various supplements. In the case in which only bonemeal and salt were fed as supplements, Group VI, and the sheep were allowed to respond to summer and winter conditions of pasture, the difference in the mean weights of the uteri is 4·8 gms. the uteri of the veld group being heavier than those of the low level ration Group V. When a veld pastured Group VII was fed a supplementary ration of maize throughout the year in addition to the mineral lick, the mean weight of the uteri is 48·1 gms. which is 9·1 gms. in excess of the control group, and 4·2 gms. in excess of the mean weight of the uteri of sheep which had received green grazing and a constant supply of mineral lick throughout the year.

It appears from the above results that nutrition affects the weight of the uteri of sheep.

TABLE XI.

Sexual Season, 1934.

Group.	(*a*) No. of sheep.	No. of sheep exhibiting oestrus.	Mean No. of dioestrous cycles.	Duration of season.	
				Range.	Mean.
				days.	days.
I.................	10	9	5·8	21–286	111·8
II...............	10	9	4·7	35–174	117·2
III..............	9	8	3·2	1–142	62·9
IV..............	9	7	2·9	1–117	43·0
V................	7	5	7·4	62–185	101·6
VI..............	9	9	9·2	102–244	183·2
VII.............	10	10	9·3	1–291	199·1
VIII............	10	10	13·3	154–280	230·4

NOTE.—(*a*) All the sheep in certain of the groups were not slaughtered for Experiment 2.

Due to the influence of the presence of corpora lutea upon the weights of the ovaries (Quinlan and Maré, 1931), it is not possible to compare the mean weights of the ovaries of the groups. However, corpora do not occur in two groups, Groups I and IV; the totals of the two mean weights of the ovaries of these groups are 1·16 and 1·19 gms. respectively.

As the dimensions of the ovaries are affected by the presence of follicles and corpora lutea (Quinlan and Maré, 1931), a comparison of measurements would be of no value.

Excepting in the case of Group III, the average number of Graafian follicles present in the ovaries does not vary greatly. Previous attention was drawn to the comparative inactivity of Group III during the last sexual season (Table XI); the average number of follicles distinguished in two ovaries is 11·7. On the other hand, Group IV was less active during the last sexual season and the average number of follicles observed in the ovaries is 16·3. The ovaries of the most sexually active groups contain an average of 17·5 and 18·1 follicles.

The size of the largest follicles varies from 0·2 – 0·5 cm. and 0·4 to 0·8 cm. Only one follicle at the point of rupture was seen (Appendix 2, Group VII, Sheep No. 15351). It will be seen by examining the details in Tables II to IX, that in many cases the ovaries of sheep which had not shown oestrus for long periods contained follicles measuring 0·5 and 0·6 cm. Grant (1934) states that "It is not yet known whether follicles are constantly growing and regressing during anoestrum or whether follicular development is simply arrested". No evidence has become available from these examinations as to what actually takes place. It may be thought improbable that the development of follicles, which are half the size of mature follicles, would be arrested and that they could possibly remain unchanged for such long periods of time, awaiting the renewal of the increased activity of the ovaries. It may be considered more likely that follicular development during anoestrum is very slow and that regression takes place when the follicles have reached about half the size of mature follicles.

Grant's (1934) observations with Scottish sheep reveal that ovulation may occur without the exhibition of oestrus at the beginning and during the latter part of anoestrum; the author refers to these as spurious ovulations. It would appear from the results reported here on Merino sheep that such ovulations are of constant occurrence. By consulting Tables II to IX, it will be seen that corpora lutea of varying sizes are found in the ovaries of sheep which had not shown oestrus for periods varying from 38 to 413 days, many of which occur within the limits of the normal anoestrous period.

No corpora lutea are present in the ovaries of the sheep in Group I, but spurious ovulations had occurred in five cases in Group II, and the previous remarks upon the results reflected in Table X were somewhat in favour of the latter group. Although the sexual history of Group III during the last sexual season reveals poor activity of the sheep (Table XI), corpora lutea were found in the ovaries of two sheep (Table X). In Group IV, which exhibited least sexual activity during the last sexual season (Table XI), no corpora were present. In Group V a corpus luteum was found in each of the ovaries of one sheep, No. 15329 (Table VI), and oestrus had not been observed in this sheep for 413 days.

In contrast to the above low level ration groups, the pasture groups appear to have experienced a larger number of spurious ovulations during anoestrum. In the control group, spurious ovulations occurred in five out of nine cases, in Group VII in five out of seven cases, and in Group VIII in six out of nine cases (Tables VII, VIII, and IX).

It appears from the above, that the more active groups during the sexual season, experienced more spurious ovulations during the anoestrous period.

An interesting feature of the presence of corpora lutea in the ovaries of the sheep during anoestrum or during prolonged periods of inactivity, is that, in the great majority of cases, only one corpus is present. In Group V, Sheep No. 15329, two corpora of approximately equal size are present, one in each of the ovaries; these are considered to be the corpora lutea of a double ovulation (Table VI). In Group VII, in each of two cases two corpora were found present; there is no doubt that in each case these are corpora lutea I and II. In the cases in which only one corpus is present, the body varies from the size and appearance of a recently formed corpus luteum to that of a minute corpus of a previous interovulation period (Quinlan and Maré, 1931). In such instances, in fifteen out of twenty-two cases the corpora are less than half the size of a fully developed corpus luteum. The circumstances suggest that, during anoestrum and abnormally long inactive periods, ovulation occurs without the exhibition of oestrus, but the periods at which such ovulations take place are not necessarily at the beginning or towards the end of the anoestrous period. It is apparent that, in the great majority of cases, successive spurious ovulations do not occur.

Conclusions.

1. The ovaries of 69 Merino sheep were examined during the anoestrous period; the weights of the uteri were recorded. The sheep had been subjected, for prolonged periods, to treatments involving low level rations in dry-lot and supplementary feeding on pasture.

2. During the anoestrous period, the ovaries of sheep subjected to all treatments are not static; this is true also of the ovaries of sheep maintained only on teff hay, bonemeal and salt for 520 days.

3. In certain cases, the ovaries are quiescent only to the extent that normal or complete ovarian activity is restricted. Gradual development of the Graafian follicles takes place until the follicles are approximately half the normal mature size, when development is arrested; at this stage either regression takes place, or the follicles remain in the partially developed stage for long periods. This condition occurs in sheep on low level rations, in sheep on unsupplemented pasture, in sheep maintained in good condition on pasture supplemented with the continuous feeding of concentrates (maize), and in sheep on supplementary green feed (cereals) during the dry autumn and winter months.

4. Cases exist in which ovulation occurs during the anoestrous period, or during prolonged periods of the absence of oestrus. Such spurious ovulations do not occur only at the beginning or at the end of the anoestrous period. Spurious ovulations occur in cases in which oestrus has not been observed for over a year.

(*a*) The number of cases in which ovulation occurs during anoestrum is not entirely dependent upon the level of feeding. Spurious ovulations occur even when Merinos have been maintained at a low level weight for extended periods.

(*b*) The inclusion of bonemeal in the mineral (salt) lick of sheep on a low level ration of maize and teff hay, results only in partial development of the follicles but no spurious ovulations. The exclusion of bonemeal from the ration results in the occurrence of spurious ovulations in 50 per cent. of cases.

(*c*) The exclusion of bonemeal and the inclusion of a protein rich concentrate (cotton seed meal) in a similar low level ration to the above (*b*), results in the partial development of the follicles, while spurious ovulations occur in approximately 22 per cent. of cases.

(*d*) The feeding of sheep on roughage (teff hay) and a bonemeal and salt lick, results in a more restricted partial development of the Graafian follicles and spurious ovulations do not occur.

(*e*) In sheep maintained under natural or untreated conditions, thus being allowed to react in body weight to the extremes of summer and winter grazing, the development of the follicles is not restricted at an early stage, and approximately 55 per cent. of cases experience spurious ovulation.

(*f*) In sheep maintained in good condition on pasture throughout the year by continuously supplementing with concentrates (maize), spurious ovulations occur in approximately 86 per cent. of cases.

(*g*) In sheep provided with green grazing throughout the year, spurious ovulations occur in approximately 66 per cent. of cases.

5. Successive spurious ovulations seldom occur during the anoestrous period, although such activity takes place in sheep which are maintained in good condition throughout the year as under the above Section 4 (*f*). In general, little development of the Graafian follicles is found in instances in which the corpora lutea are in advanced stages of regression.

6. In cases in which follicular development is greatly restricted during the anoestrous period, the ovaries are small and light; pairs of ovaries weigh 0·51 and 0·38 gms. When greater follicular development takes place and when spurious ovulations occur, the ovaries are larger and heavier and they approach the normal evidenced during the sexual season. When spurious ovulation occurs, the size and weight of the ovary is influenced largely by the stage of the corpus luteum present.

7. A consideration of the sexual histories of the sheep indicates that those which are more active during the sexual season are more likely to experience spurious ovulations during anoestrum.

8. Low level rations fed over extended periods, inhibit the development of the uteri of young sheep.

(*a*) The inclusion of bonemeal in such rations, reflects no advantage.

(*b*) The exclusion of bonemeal and the inclusion of a protein rich concentrate (cotton seed meal) in such rations, result in a reduced weight of the uterus.

(*c*) The feeding of a carbonaceous roughage (teff hay) and no concentrates, but a lick of bonemeal and salt, results in a further reduction of weight of the uterus.

9. The supplementary feeding of sheep on pasture results in appreciable increases in the weight of the uterus.

10. There is no obvious relationship between the length of the period of sexual inactivity and the weight of the uterus, that is, the weight of the uterus does not decrease as the inactive period progresses.

EXPERIMENT 3.

THE DURATION OF THE PHASES OF THE DIOESTROUS CYCLE IN MERINO SHEEP.

The object of the experiment was to determine the duration of oestrus, dioestrum, and the dioestrous cycle in Merino sheep.

Materials and Methods.—Thirty-nine ewes of good Merino type were used in this experiment; their ages ranged from 3 to 7 years. Most of the sheep had been bred at the Experiment Station, others had been on the Experiment Station for at least a year; the sheep may, therefore, be considered to have been acclimatized.

The 39 sheep reported upon were obtained from a flock of 350 ewes by testing the latter flock for oestrus with vasectomised teasers at 7 a.m. and 5 p.m. on April 10th, 11th, and 12th, 1935. This oestrus is referred to as the preliminary or first oestrus (Table I). The ewes showing oestrus on the three dates mentioned, were drafted into a separate flock, which was run in a paddock near the observation yards. During the interoestrous period, the experimental flock was brought to the observation yards once daily and tested for oestrus until April 23rd.

On April 23rd, one ewe (No. 32657) was found to be in oestrus at 7 a.m. and from this time and date testing for oestrus was carried out at 3-hour intervals day and night, the flock being divided at the time of testing into groups of ten. Ten vigorous teasers, working in relays of five, were used to make the observations. The intensive observations were carried out until 6 a.m. on 2nd May, 1935, when all but one ewe (No. 32500) had shown and completed oestrus; oestrous observations on this ewe were continued at 12-hour intervals until she showed oestrus on 4th May, 1935.

Provision had been made to accommodate the experimental ewes in a large yard during the intensive period of testing for oestrus. The yard was supplied with the required facilities for feeding and watering. The sheep were fed on a ration of 8 ounces of crushed maize, teff hay ad lib, and a lick of 3 parts of bonemeal and 1 part of salt was supplied. The small pens of the observation yards permitted easy handling; at no time did the handling appear to fatigue the sheep. At night, observations were carried out with the aid of lanterns and electric torches. The observations were supervised at all times by a European stock foreman or by the author; a native assistant was in constant attendance.

When testing for oestrus, a ewe was not considered to be in oestrus unless she definitely stood for service. It will be seen later that the onset of oestrus was found to be abrupt, but that the passing off of oestrus was gradual or indefinite. During the latter stage of oestrus, great care in testing had to be observed. In order to improve the thoroughness of the observations, the ewes in oestrus were kept separate, which permitted testing these ewes individually at each 3-hourly testing. In the case of ewes about to pass out of oestrus, a reluctance to stand for the teaser was found, but coaxing by the teaser induced the ewes to stand and to be served; in these cases oestrus was considered to be present. In recording the presence of oestrus the sign " O " was used. In other cases, ewes passing out of oestrus were found to circle about the teaser; they did not run away, but would not stand to be mounted. It was observed that teasers used a considerable amount of coaxing with such ewes before attempting to mount. In such cases, when the teaser had attempted to mount the ewe four times without success, the ewe was considered to be passing out of oestrus and, in recording such observations, the sign " O➤ " was used. It was observed that ewes that had definitely passed out of oestrus did not stand for coaxing by the teaser, but they jumped forward and ran away. Further, it was observed that ewes definitely showed preference for particular teasers and this was especially the case when the former were passing out of oestrus. In order to overcome any irregularity due to this peculiarity, a very vigorous teaser, which was observed to be favoured by ewes, was kept for finally testing the " non-oestrus " ewes, any doubtful cases, and particularly those ewes which were passing out of oestrus. When no oestrus was present, the sign " — " was used to record the observation. Ewes passing out of oestrus were tested individually for four periods, that is, for 12 hours, after oestrus was last observed.

During the interoestrous period of the second dioestrous cycle, that is of the so-called second oestrus, the experimental ewes were kept near the observation yards, and oestrous observations were made twice daily at 7 a.m. and 5 p.m. The procedure appeared to be necessary to ensure that no ewe with a short dioestrum and a short subsequent oestrus was missed. Such testing was continued up to 7 a.m. on May 11th.

On May 11th, one ewe (No. 32657) was found to be in oestrus at 7 a.m., and from this time and date oestrous observations were made at 3-hourly intervals day and night, the flock being similarly divided and the particular procedures being identical to those employed during the observations of the previous intensive testing for the duration of oestrus. Such observations were continued until 12 noon on May 20. One ewe, No. 32500, had not shown oestrus up to that date; the testing for oestrus of this ewe was continued beyond that date at 12-hour intervals until oestrus was observed on 28th May, 1935.

The intensive testing at each 3-hour interval took from ½ hour to 1½ hours depending upon the number of sheep and especially the number requiring individual testing.

Results.

Details of the observations are presented in Table I.

The preliminary, or first oestrus, was used merely as a guide to indicate the approximate date on which subsequent oestrus was likely to occur.

Table I, columns 4 and 10, 2nd and 3rd exhibitions of oestrus, contain the dates on which oestrus was observed during the intensive testing for oestrus, while the specific times of the duration of oestrus are indicated in the columns adjacent and to the right of the former columns. The signs which were explained in the previous section, indicate the presence, gradual passing off, and absence of oestrus.

In the columns of Table I containing the specific times of the duration of oestrus, it will be seen that certain oestrous periods were interrupted by the absence of oestrus at one or more periods of 3-hourly testing. In such cases, the uninterrupted period has been considered as the true duration, and the additional period or the resumption of oestrus is indicated in brackets (Table I ,columns 9 and 15).

The interrupted oestrous periods also cause inconsistency in the computation of dioestrum; in such cases dioestrum has been taken to extend from the complete cessation of oestrus up to the onset of the next oestrus (Table I, columns 16 and 17). However, the interrupting or non-oestrous periods occurring during the latter part of certain oestrous periods have been indicated in brackets (Table I, column 17) and they have been taken into account in the further analysis of the data. (Table II.)

The duration of the dioestrous cycle has been taken as the period from the onset of the second oestrus up to the onset of the third oestrus (Table I, columns 18 and 19).

The further analyses of the data presented in Table I are given in Tables II to V.

Discussion.

The Symptoms of Oestrus.—McKenzie and Phillips (1930) and Grant (1934) have indicated that the symptoms of heat in the ewe are less marked than in the cow (Hammond, 1927) and in the sow (McKenzie, 1926). The symptoms in Scottish sheep have been described in great detail by Grant, whose observations were made by means of a "keeled " ram.

The three-hourly observations made for obtaining the information reported in this experiment afforded ample opportunity for observing the mutual behaviour of ewes and rams or teasers. Most of the observations of Grant (1934) have been confirmed in the case of the Merino; however, the Merino ewe appears to be somewhat conservative in that, while some ewes may approach the ram and all ewes look back and vibrate their tails when the ram displays interest, no ewes have been observed to " pet " the ram before and after service, to lick his face, and to rub their heads against his side. However, the present author has seen a Merino approximately 12 hours in heat, butt a teaser serving another ewe.

TABLE II.

Frequencies of the Duration of Oestrus in Merino Sheep.

Hours	1–2	3–5	6–8	9–11	12–14	15–17	18–20	21–23	24–26	27–29	30–32	33–35	36–38	39–41	42–44	45–47	48–50	51–53	54–56	57–59	Total
Frequencies	1	0	0	0	0	2	5	9	10	7	11	10	9	2	3	2	2	0	0	1	74

TABLE III.

Frequencies of the Duration of Dioestrum in Merino Sheep.

Days and Hours	11–0	14–9	14–12	14–15	14–21	15–0	15–3	15–6	15–9	15–12	15–15	15–18	15–21	16–3	16–6	16–9	16–12	16–15	16–21	17–0	17–6	Total
Frequencies	1	1	1	1	2	3	1	6	2	3	5	1	1	1	1	1	2	1	1	1	1	37

TABLE IV.

Frequencies of the Duration of the Dioestrous Cycle in Merino Sheep.

Days and Hours	12–12	15–21	16–6	16–9	16–12	16–15	16–18	16–21	17–0	17–3	17–6	17–9	17–21	18–0	18–9	Total
Frequencies	1	3	2	1	5	4	4	4	2	2	2	1	3	2	1	37

TABLE V.

The Duration of the Phases of the Dioestrous Cycle.

	2nd and 3rd Oestrus Periods.				Dioestrum.				Dioestrous Cycle.	
	*a**	*b*	*c*	*d*	*e**		*f*			
Range of variation............	hours 1–57	hours 1–58·5	hours 15–57	hours 15–58·5	days 11–0	hours 17–6	days —	hours —	days 12–12	hours 18–9
Mean.........................	29·3	29·7	29·7	30·1	15	11·3	15	12·0	16	18·6

*NOTE: (*a*) The abnormal oestrus of one hour, sheep No. 38516, has been included and in cases in which oestrus was interrupted, only the uninterrupted period of oestrus was considered.

(*b*) The abnormal oestrus of one hour, Sheep No. 38516, has been included and in cases in which oestrus was interrupted, the period of oestrus following the interruption was included.

(*c*) The abnormal oestrus of one hour, Sheep 38516, has been omitted, and in cases in which oestrus was interrupted, only the uninterrupted period of oestrus was considered.

(*d*) The abnormal oestrus of one hour, Sheep No. 38516, has been omitted and in cases in which oestrus was interrupted, the period of oestrus following the interruption was included.

(*e*) In cases in which oestrus was interrupted, diostrum was computed from the time of the complete cessation of oestrus which excludes the period of the interruption of oestrus.

(*f*) In cases in which oestrus was interrupted, diostrum was computed from the time of the complete cessation of oestrus and the period of interruption was added.

Changes in the external genitalia of sheep in oestrus have been described by McKenzie and Philips (1930) and Grant (1934). Various degrees of congestion and swelling of the vulva have been noticed and in some cases the whole tail region is involved; the vulva are moist and sometimes a slight excretion of mucous occurs. The present author examined a large number of the Merino ewes reported upon in this experiment; the examinations were made at different stages of oestrus. In very few cases a slight indication of congestion was evidenced, but no marked swelling of the external labia of the vulva and the tail region was observed, nor was there any excretion of mucus. However, it may be remarked here that, during oestrous observations upon Border Leicester-Merino crossbreds, definite swelling of the vulva was noticable during oestrus and the excretion of mucus occurred. These symptoms of oestrus appear to be characteristic of the English and Scottish breeds and their crosses but not of the Merino.

Duration of Oestrus.—The details of the duration of oestrus are given in Table I, columns 4 to 8 and 10 to 14.

It is seen that in the case of Sheep Nos. 32500 and 32657, oestrus occurred beyond the periods of intensive testing.

The onset of 73 out of 74 periods of oestrus was abrupt. At the first testing for the duration of oestrus, Sheep No. 38516 showed signs of coming into oestrus for nine hours before oestrus was definitely present. However, the individual case cited was abnormal in that the sheep remained in oestrus for less than three hours (Table I, column 5). Grant (1934) observed the abrupt onset of oestrus in Scottish sheep, but McKenzie and Philips (1930) and Quinlan and Maré (1931) consider that oestrus comes on gradually for several hours. McKenzie and Philips state that the period of becoming receptive to the ram ranges from 0-15¼ hours.

The contention of Grant (1934) is upheld that the decision as to whether a ewe is receptive depends a great deal upon the persistency of the teaser. In all cases of doubt in this experiment, the most vigorous teaser was used. The author has seen a ewe walk out from a small group of ewes and teasers to a dividing fence beyond which the vigorous teaser was working; when the ewe was put through to the adjoining yard, she immediately stood for service by the vigorous teaser.

The observations of Grant (1934) and Quinlan and Maré (1931) that the passing off of oestrus is gradual have been confirmed in this experiment; however, the latter reveals considerable variation. The duration of two periods of heat of 37 sheep was studied. Out of a total of 74 heat periods, in approximately 42 per cent. of cases the termination of oestrus was abrupt; in approximately 36 per cent. of cases the passing off of oestrus was gradual and regular; in the remaining cases some or other form of interruption or irregularity occurred. The symbols used indicate that, in certain instances, sheep were found to be passing out of oestrus, or even definitely out of oestrus, for three or as long as nine hours, after which oestrus was observed to have returned. The gradual passing off of oestrus generally lasted for from three to six hours.

It is seen from Table II, that the range of variation of the duration of oestrus is considerable; the mode falls within the class of thirty to thirty-two hours; but in 77 per cent. of cases, the duration of oestrus is twenty-four hours and longer. The range of variation is given accurately in Table V; when only the uninterrupted periods are considered, the maximum duration is fifty-seven hours, and, with the exclusion of one exceptionally short period of less than three hours, the shortest duration of oestrus is fifteen hours. The mean varies according to the types of computations made, but the differences reflected are not great and means of approximately twenty-nine and thirty hours can be considered (see notes to Table V). These durations of oestrus are somewhat shorter than those observed by Quinlan and Maré (1931) in Merino sheep; the latter authors observed an average duration of forty hours, the shortest twenty-four hours, and the longest ninety-six hours. McKenzie and Philips (1930) found the mean duration of oestrus in Hampshires, Shropshires, and Southdowns to be 30·7, 26·3, and 24 hours respectively, while Grant (1934) has reported a period of 35 hours for Cheviots.

Duration of Dioestrum.—Dioestrum is the period from the cessation of oestrus up to the time of the commencement of the next oestrus.

Table III indicates the frequencies of the duration of dioestrum in Merino sheep. The range of variation is seen to be from 11 days to 17 days 6 hours and the mode is 15 days 6 hours. The mean duration of dioestrum is 15·5 days (Table V) and, in approximately 73 per cent. of cases, the duration of dioestrum exceeds 15 days.

Duration of the Dioestrous Cycle.—The periodicity of oestrus has been found to vary considerably (Quinlan and Maré, 1931 and McKenzie and Philips, 1930); dioestrous cycles as short as 6 and 7 days have been reported. The shortest cycle observed in this experiment is 12 days 12 hours, and the longest 18 days 9 hours (Table I columns 18 and 19); the mode is 16 days 12 hours (Table IV), and the mean 16 days 18·6 hours. In 51·4 per cent. of cases the duration of the dioestrous cycle is 16·5 to 17 days. The mean cycle is somewhat shorter than that reported by Quinlan and Maré (1931) for Merino sheep. McKenzie and Philips observed an average cycle of 16·6 days in Hampshires, Shropshires, and Southdowns, and Grant (1934) recorded a cycle of 16·4 days in Scottish breeds and crosses.

In the observations reported here, no cases of " silent " oestrus occurred. Hammond (1927) has suggested that in cattle such cases may be due to either abnormally short durations of oestrus which are missed when observations are made at 12 or 24 hour intervals, or that exceptionally feeble heat periods may be experienced. However, it appears that even when continuous testing with " keeled " rams is practised, in certain cases oestrus is not exhibited regularly at normal intervals. (McKenzie and Philips, 1930; Casida and McKenzie, 1932; Grant, 1934).

Conclusions.

1. The duration of oestrus, dioestrum, and the dioestrous cycle of 37 Merino ewes, was determined by testing for oestrus at three hourly intervals during the periods of heat and at twelve hour intervals during dioestrum.

2. The duration of oestrus varies considerably:—

   (*a*) Abnormal periods of less than 3 hours duration may occur. Periods as long as 58·5 hours may be expected.

   (*b*) The mode falls within the class 30 to 32 hours and in 77 per cent. of cases the duration of oestrus is 24 hours and over.

   (*c*) The mean duration of oestrus is approximately 30 hours.

3. Appreciable variation of the length of dioestrum occurs:

   (*a*) The range of variation extends from 11 days to 17 days 6 hours.

   (*b*) The mode of the duration is 15 days 6 hours and in approximately 73 per cent. of cases dioestrum exceeds 15 days.

   (*c*) The mean duration is 15·5 days.

4. Dioestrous cycles only of normal length occur:

   (*a*) The range of variation extends from 12 days 12 hours to 18 days 9 hours.

   (*b*) The mode of duration is 16·5 days, and in approximately 51 per cent. of cases oestrus recurs after 16·5 to 17 days.

   (*c*) The mean duration of the dioestrous cycle is 16·8 days.

5. During oestrus, Merino sheep do not reveal marked swelling of the external labia of the vulva, nor is there any excretion of mucus.

6. The onset of oestrus in Merino sheep is abrupt.

7. The termination of oestrus in Merino sheep may be abrupt or gradual. On the other hand, oestrus may pass off completely or partially for from 3 to 9 hours at the end of the oestrous period, after which a resumption of oestrus may occur, the return of oestrus being definite or feeble and its renewed duration may be from 3 to 6 hours.

   (*a*) In approximately 42 per cent. of cases, the termination of oestrus is abrupt.

   (*b*) In approximately 36 per cent. of cases, the passing off of oestrus is gradual.

   (*c*) In approximately 22 per cent. of cases, the latter portion of the oestrous period is interrupted by the total absence of oestrus or by the exhibition of "feeble" oestrus.

EXPERIMENT 4.

THE PERIOD OF THE ABSENCE OF OESTRUS AFTER PARTURITION IN MERINO SHEEP.

The duration of the period of sexual inactivity after parturition is of considerable practical interest. This phase of the subject of ovarian activity has received attention by certain investigators.

Oestrus has been observed to occur 24 hours after abortion (Nichols, 1924). Normal oestrus has been observed in Merino ewes 17 and 21 days after the birth of still-born lambs by Quinlan and Maré (1931) and van Rensburg (1935). The former authors have found that ovulation may occur 10 to 15 days post partum.

Preliminary observations made by the author, indicated that the duration of the period of sexual inactivity after lambing in Merino sheep was prolonged under the conditions of the eastern Transvaal.

In farm practice, the procedure is to regulate lambing to occur at a time when natural conditions are most favourable. When lambing takes place during the spring months, pasture is abundant, but heavy infections of young lambs with internal parasites have caused greater preference to be given to autumn lambing in Merino studs and flocks. The problem of changing over from spring to autumn lambing appears to be one of great practical interest in certain areas. The postponement of mating from the autumn to the spring would mean the loss of 7 to 8 months, so that the possibility of rapid alteration of the mating season would depend entirely upon the onset of sexual activity after lambing.

The object of this experiment was to determine the duration of the period of the absence of oestrus after parturition when lactation is terminated by early weaning and when lactation is allowed its normal course.

Materials and Methods.—Three groups of mature Merino ewes, which had lambed the year previous to their inclusion in the experiment, were used for the observations. Preliminary observations were made on 13 sheep in Group I which lambed during July and August, 1931; further observations were made on 9 sheep in each of Groups II and III, which lambed during September, 1933. The sheep in Group II were ewes the lambs of which had died within three days after birth. The lambs of Groups I and III were weaned when they were 4½ to 5 months of age.

Due to the lack of green winter pasture, the ewes in Group I were fed 6 ounces of maize with maize silage and teff hay. As spring pasture became available, the feed was decreased and, eventually, withheld; the feeding of silage was discontinued on 1.10.31, and the remaining feeds were withdrawn on 20.10.31.

Groups II and III were grazed on green oats for two months prior to the commencement of lambing and fresh spring pasture became available during the first week of September, or soon after the sheep started lambing.

A lick consisting of two parts of bonemeal and one part of salt was self-fed to all groups. The general methods of management, indicated under the corresponding section of Experiment 1, were applied to these groups.

No weight records were taken of Group I. Groups II and III were weighed after 12 to 14 hours starvation at 14 day intervals; in the former case, weighing was commenced approximately one month after lambing, and, in the case of Group III, about two months after lambing.

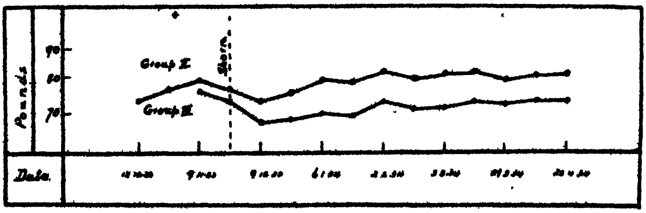
The groups were grazed near the observation yards to which they were brought daily for oestrous observations. Oestrous observations on Group I were continued for only a month after sexual activity had commenced; during this period all the sheep had exhibited oestrus; the occurences of oestrus other than the first were not considered. In the case of Groups II and III, oestrous observations were continued for several months of the sexual season, or until the majority of the members of the groups had completed several dioestrous cycles. The observations on the latter two groups were discontinued on 30.4.34, but individuals that had not shown oestrus by that date were kept under daily observation for oestrus until such time as oestrus was exhibited. Three sheep in Group III failed to show oestrus throughout the entire period of the observations; they were, eventually, slaughtered for macroscopic examination of their ovaries.

Results.

The weight records of Groups II and III are given in Appendix 3, Tables I and II. The average weights of the groups have been computed and from these the accompanying Diagram 3 has been constructed.

DIAGRAM 3.

EXPERIMENT 4.



Mean weight of groups at 14 day intervals.

The results of the oestrous observations on Groups II and III are given in Appendix 3, Tables III and IV. The sexual histories of individual ewes in Groups I, II, and III are given in Tables I, II and III respectively of the text.

TABLE I.

Group I.

The Sexual History of Breeding Ewes.

Sheep No.	Date of lambing.	Date of first oestrus.	Period between lambing and first oestrus.	Period between lambing and termination of observations.	
				Duration.	No. of dioestrous cycles.
			days.	days.	
368	3.8.31	22.2.32	203	—	—
100	10.8.31	4.3.32	207	—	—
13413	25.8.31	23.2.32	182	—	—
15356	18.8.31	4.3.32	199	—	—
18443	11.8.31	15.2.32	188	—	—
19432	6.8.31	23.2.32	201	—	—
21495	7.8.31	19.3.32	225	—	—
21519	27.7.31	16.2.32	204	—	—
21658	15.8.31	18.2.32	187	—	—
25873	10.8.31	23.2.32	197	—	—
25921	8.8.31	15.3.32	220	—	—
25930	10.8.31	7.3.32	210	—	—
25944	15.8.31	24.2.32	193	—	—
Total	—	—	2616	—	—
Average	—	—	201·2	—	—

TABLE II.

Group II.

			days.	days.	
25914	2.9.33	5.11.33	64	240	9
22031	8.9.33	13.1.34	127	234	5
22035	17.9.33	3.1.34	108	225	7
35610	22.9.33	18.2.34	149	220	4
35659	8.9.33	1.3.34	174	234	3
35701	18.9.33	10.5.34	234	234	1
35741	7.9.33	7.2.34	153	235	4
35755	18.9.33	19.1.34	123	224	6
35978	29.9.33	10.12.33	72	213	8
Total	—	—	1204	2059	47
Average	—	—	133·8	228·8	5·2

TABLE III.

Group III.

Sheep No.	Date of lambing.	Date of first oestrus.	Period between lambing and first oestrus.	Period between lambing and termination of observations.	
				Duration.	No. of dioestrous cycles.
18449	20.9.33	11.2.34	144	222	5
35628	9.9.33	16.2.34	160	233	2
35656	2.9.33	(no oestrus)	—	347	Slaughtered : 15.8.34
35706	13.9.33	(no oestrus)	—	352	Slaughtered : 22.6.34
35712	29.9.33	13.3.34	165	213	3
35731	10.9.33	(no oestrus)	—	355	Slaughtered : 22.6.34
35734	2.9.33	22.2.34	173	240	5
38518	20.9.33	5.1.34	107	222	6
38521	28.9.33	18.3.34	171	214	2
Total	—	—	920	1344	23
Average	—	—	154·0	224·0	3·8

It will be noticed in Appendix 3, Tables III and IV, that four sheep, Group II, No. 35701, and Group III, Nos. 35656, 35706, and 35731, did not show oestrus during the period of oestrous observations. The observations on these sheep were extended and Sheep No. 35701 eventually showed oestrus after a total period of 234 days (Table II). The remaining three sheep did not show oestrus after a total period of testing of 347 and 355 days (Table III); these sheep were slaughtered for the examination of their ovaries on the dates indicated in the latter table, and the results of such examinations are given in Appendix 3A, from which Table IV of the text has been constructed.

Discussion.

In the case of Group I, the lambs were born during the month of August (1931) and they were weaned when 135 to 150 days old (Table I). The lambs of Group II and III were born during September (1933); those of Group II died within the first week after birth while those of Group III were weaned when 135-150 days old.

Although no weight records were taken of the Group I ewes, it was recorded that the sheep showed satisfactory improvement of condition during the period of observation. From the weight records of Groups II and III (Appendix 3, Tables I and II), from which Diagram 3 has been constructed, it will be seen that the Group II sheep show an immediate recovery in weight after lambing, and, although a slight drop in weight occurs before shearing, very rapid improvement takes place after shearing. From the beginning of February, a more or less constant weight is maintained. The sheep

TABLE IV.

The Examination of Ovaries of Inactive Sheep.

Sheep. No.	Age.	Condition.	Weight.	Period between lambing and date of slaughter	Ovaries.				*Graafian follicles.*			*Corpora Lutea.*	
					Left.		Right.		No observed.		Largest.	I.	II.
					Weight.	Size.	Weight.	Size.	Left. ovary.	Right. ovary.			
	years.		lb.	days.	gm.	cm.	gm.	cm.			cm.	cm.	cm.
35706	6	Good	75·0	352	0·55	1·5×1·0×0·7	0·97	1·7×1·0×0·9	2	1	0·4	1·0×0·9	0
35731	6	Fair.	66·5	355	0·56	1·5×1·0×0·7	0·60	1·2×1·2×0·7	2	2	0·3	0	0
35656	8	Poor	66·0	347	0·89	1·8×1·2×0·7	0·48	1·4×0·9×0·7	5	7	0·5	0	0

in Group III do not recover so rapidly after shearing, and, in spite of the fact that their lambs had been weaned at the beginning of February, they also maintain a more or less constant weight from the beginning of that month. The difference in weight is 3 pounds in favour of Group II at the beginning of November, 1933, but at the time of the termination of the observations, at the end of April 1934, the difference in weight increases to 9 pounds. As the sheep in Group III were in fair to good condition, the lighter weight of these sheep cannot be considered to have affected their sexual activity (Experiment 1A).

The occurrences of oestrus of Groups II and III are given in Appendix 3, Tables III and IV. It is seen that several of the sheep in Group II started showing oestrus before those in Group III, and that greater sexual activity was exhibited in both groups from February, or when the sheep showed no further improvement in condition.

The sexual histories of the sheep in Groups I, II, and III have been summarised and presented in Tables I, II, and III of the text.

It is seen that the sheep in Group I were sexually inactive during the period of rearing their lambs and for approximately 50 days beyond this period. The period of sexual inactivity after parturition ranges from 182 to 225 days, the average duration being approximately 201 days. The sheep in Group III had received similar treatment with respect to the weaning of lambs. In this case, the range of variation of the period of sexual inactivity after parturition is 107 to 173 days, but only approximately 67 per cent. of the group had shown oestrus, although oestrous observations on the remainder had been extended for close on a year. In Group III, the average duration of the inactive period is 154 days or approximately the length of the lactation period. No explanation can be given for the longer period of inactivity experienced by the sheep in Group I.

In the case of Group II, the lambs of which had been weaned almost immediately after parturition, the range of variation of the duration of the sexually inactive period is 64 to 234 days, the average being 133·8 days. The latter figure is greatly influenced by one case in which the inactive period is 234 days.

The increased sexual activity of Group II as compared to Group III, is further indicated by the number of dioestrous cycles experienced. In Group II, the cycles range from 1 to 9, the average being 5·2 cycles during an average period of 228·8 days, while in Group III, the range is from 2 to 6, the average being 3·8 cycles during an average period of 224 days.

The results of the examinations of the ovaries of the three inactive sheep in Group III indicate, that one sheep had ovulated recently, as a large corpus luteum was present. The numbers of Graafian follicles readily distinguishable in the ovaries of these sheep are small (Table IV). The details of the macroscopic examinations of the ovaries are given in Appendix 3a.

It appears from the above results that, in cases in which lactation is allowed to run its normal course, the onset of sexual activity is later than in cases in which lactation is terminated at an early stage.

In connection with the influence of lactation upon ovarian activity, Parkes (1929) has demonstrated by practising ovariectomy, that the inhibition of oestrus during lactation is set up through the ovary and that the absence of oestrus is not due to the heavy drain upon the metabolism resulting from lactation. Crew and Mirskaia (1930 a), reporting upon the reproductive rate in the mouse, indicate that the non-suckling female is capable of giving birth to twice as many offspring in a given period of time as can the suckling mouse. Crew and Mirskaia (1930 b), in discussing the lactation interval in the mouse, contend that "suckling is the agent primarily responsible for the maintainance of the lactation interval, and, when it is removed, no matter at what stage of the interval, the interval terminates and the oestrous phases replace the reproductive ". It is further contended, that the transformation of the corpus luteum of pregnancy to that of lactation is brought about by the action of the pituitary to the stimulus of suckling and that, endocrimologically, the conditions of pregnancy and of lactation are very similar, if not identical.

The detailed studies of Quinlan and Maré (1931) on the changes in the ovary of Merino sheep during pregnancy and early lactation indicate that, immediately after parturition, there is a rapid decrease in the size of the corpus luteum vera, and that one or more Graafian follicles rapidly develop in preparation for the first post-parturition ovulation. These authors state that, while ovulation may occur 10 to 15 days following normal parturition, such ovulation is not accompanied as a rule by the physiological exhibition of heat when the ewe suckles her lamb. It will be revealed in a later section of this thesis, that, in certain cases, normal oestrus and ovulation may occur during the early stages of lactation in Merino ewes (Part 2, A). It may be remarked here that it is the practice of certain Merino stud breeders to wean the lambs at 3 months of age; the purpose of this procedure is to permit the ewes a longer period of rest in preparation for the next mating season.

The following facts have not been established with regard to Merino sheep:

(1) Whether, as a general rule, spurious ovulations occur during the early stages of lactation.

(2) At what stage of lactation normal oestrus and ovulation occur in areas where continuous sexual activity is experienced throughout the year, and whether, in such areas, the onset of sexual activity is hastened by the early termination of lactation.

(3) Whether the changes in the ovary after parturition differ in areas where a part of the period of parturition and the whole of lactation occupy the period equivalent to that of anoestrum in the non-pregnant ewe.

(4) Whether, in areas where a prolonged anoestrous period is experienced, the period of time before the onset of ovarian activity differs when lambing occurs during the autumn rather than during the spring.

Conclusions.

1. Observations upon the onset of sexual activity after parturition were made with 22 Merino ewes, the lambs of which were weaned at approximately 5 months of age, and with 9 Merino ewes the lambs of which had died within 7 days of birth.

2. Sheep that lamb during the spring and that are allowed to rear their lambs to the age of 5 months do not exhibit oestrus during lactation.

Although in relatively few cases oestrus may be exhibited as soon as 3·5 months after parturition, in approximately 87 per cent. of cases the period during which oestrus remains absent exceeds 150 days.

3. Sheep that lamb during the spring and the lambs of which are weaned immediately, experience a relatively short inactive period after parturition.

In such cases, oestrus may be expected to occur 2 months after parturition, and in 67 per cent. of cases the onset of sexual activity occurs within 150 days after parturition. Once sexual activity has commenced, normal dioestrous cycles occur.

4. In cases of prolonged inactivity, the ovaries may be in a quiescent state, or occasional spurious ovulation may occur.

5. The presence of suckling delays the onset of the sexual season, although the absence of lactation does not entirely eliminate the anoestrous period experienced by sheep which lamb in the spring under eastern Transvaal conditions.

EXPERIMENT 5.

THE SEXUAL SEASON OF CROSSBRED SHEEP.

The restricted annual sexual activity of Merino sheep reported in the preceding experiments, led to a consideration of the sexual activity of certain crossbred sheep available at the Experiment Station, namely, Suffolk-Blackhead Persians and Blackhead Persian-Merinos.

The Suffolk, like most British breeds of sheep, experiences a restricted annual sexual season in its home country and abroad (Heape, 1900, Marshall, 1903, 1922, Roberts, 1921, Cole and Miller, 1933). Evidence is produced in a subsequent section of this thesis which indicates that, in the southern hemisphere, the sexual season of the British breeds of sheep conforms to the new order of the seasons of the year (Part 2, B). The Blackhead Persian is a hardy breed of sheep which has been found to be well suited to the semi-arid areas of this country. The owners of this breed maintain that these sheep are capable of being bred at any time of the year, which would indicate the existence of an extreme degree of polyoestrum. In general, crossbred sheep are early maturing and exhibit great vigour; in these respects they excel the slower maturing and less vigorous Merino.

The object of the experiment was to observe the extent of annual sexual activity exhibited by Suffolk-Blackhead Persian and Blackhead Persian-Merino crossbred sheep, and to compare the sexual activity of these crossbreds with that of Merino sheep.

Materials and Methods.—Two groups, each consisting of ten ewes, were drafted at random from the two types of crossbreds available. Observation were commenced on May 25th, 1933, and terminated on May 29th, 1934.

The Suffolk-Blackhead Persian sheep comprising Group I were mature, and they had lambed the previous season. The Blackhead Persian-Merino sheep, Group II, were bred on the Experiment Station, and they were 9 to 10 months old when they were drafted into the experiment. The Merino sheep used for the purpose of comparison constituted Group VI, Experiment 1A; this group is referred to in this experiment as Group III.

The sheep were weighed at fortnightly intervals and oestrous observations were conducted once daily. The procedure in recording these observations was identical to that given in the preceding experiments reported here.

The general management of the sheep was similar to that of the groups of sheep in Experiment 1A and it was identical in every particular to the treatment of Group VI, Experiment 1A, in that the two groups of crossbred sheep were maintained on the same natural pasture supplemented throughout the year only by a mineral lick consisting of two parts of bonemeal and one part of salt.

Result.

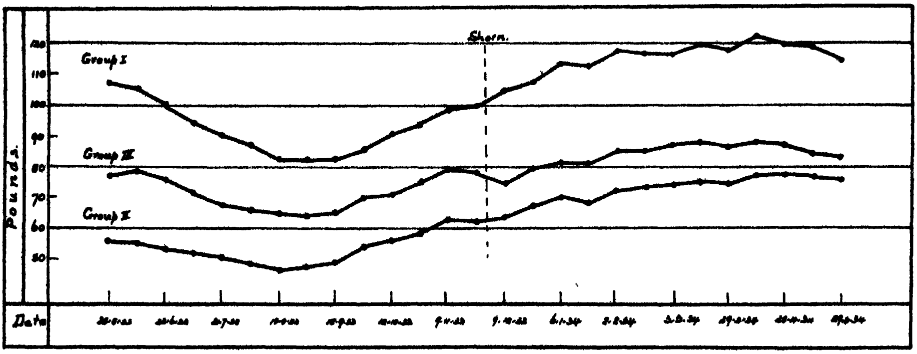
The weight records of Groups I and II, taken at 14 day intervals, are given in Appendix 4, Tables I and II. The average weights have been computed and from these Diagram 4 has been constructed. The weight curve of Group III has been constructed from the weight data of this group given in Appendix 1A, Table VI.

The oestrous observations and sexual seasons of Groups I, II, and III are given in Appendix 4, Tables III, IV, and V. In the case of Table V, the data have been taken from Appendix 1, Table XIV; only the observations for the identical period of Groups I and II have been considered, that is from 24.5.33 to 29.5.34.

Table I of the text, indicating the seasonal sexual activity of the three groups of sheep, has been constructed from Appendix 4, Tables III, IV, and V. Table II of the text giving the frequencies of the periodicity of oestrus has been compiled from data in the latter three tables.

DIAGRAM 4.

EXPERIMENT 5.



Mean weights of groups at 14 day intervals.

Photographs of Groups I and II are given in Figs. 22 and 23, and photographs of Group III are given in Figs. 11 and 12 (Experiment 1A).

Discussion.

The weight curves illustrate the reaction of the three different types of sheep in Groups 1, II, and III to the changes in the natural pasture as affected by the seasons (Diagram 4).

The mature Suffolk-Persian crossbreds, comprising Group I, lost 23·8 per cent. in weight from 25.5.33 to 18.8.33, or a period of 85 days, and, although they did not recover this loss after an equivalent period, the difference between the lowest mean winter weight and the highest mean summer weight reveals, that the sheep gained 48·6 per cent. on the former weight during a period of 239 days (Appendix 4, Table I).

The young Blackhead Persian-Merino crossbreds, comprising Group II, lost 17·4 per cent. in weight during the period of 85 days, and the difference between the lowest mean winter weight and the highest mean summer weight reveals, that the sheep gained 62·9 per cent on the former weight during a period of 239 days (Appendix 4, Table II).

TABLE I.

The Sexual season of Crossbred and Merino Sheep.

Group.	Sexual Season, 1933. May to August.			Anoestrous Period, 1933–1934. September to January.		Sexual Season, 1934. February to May.		
	No. of sexually active sheep.	No. of dioestrous cycles.		Duration (days).		No. of sexually active sheep.	No. of dioestrous cycles.	
		Range.	Average.	Range.	Average.		Range.	Average.
I	10	3—6	4·30	205—246	226·?	10	4—7	5·6
II	4	0—4	1·75	195—289 +	237·5 +	10	2—9	6·3
III*	10	1—5	3·90	118—341	204·4	9	1—7	5·2

* NOTE :—Group III is a group of Merino ewes, included for comparative purposes.

TABLE II.

Frequencies of the Periodicity of Oestrus.

Days.	Sexual Season, 1933.									Sexual Season, 1934.													Sexual Seasons, 1933 and 1934.															Total.
	15	16	17	18	19	33	34	35	36	15	16	17	18	19	20	32	33	35	38	52	54	74	15	16	17	18	19	20	32	33	34	35	36	38	52	54	74	
Group I	4	8	15	4	1	1	—	—	—	6	25	12	1	1	—	1	—	—	—	—	—	—	10	33	27	5	2	—	1	1	—	—	—	—	—	—	—	79
Group II	—	—	2	1	—	—	—	—	—	—	3	22	16	5	1	—	—	2	1	1	1	1	—	3	24	17	5	1	—	—	—	2	—	1	1	1	1	56
Group III	—	1	8	14	3	—	1	1	1	—	2	14	15	—	1	—	1	4	—	—	—	—	—	3	22	29	3	1	—	1	1	5	1	—	—	—	—	66

The mature Merino sheep, comprising Group III, lost 15·6 per cent. in weight during a period of 99 days, and the difference between the lowest mean winter weight and the highest mean summer weight reveals, that the sheep gained 36·0 per cent. on the former weight during a period of 225 days (Experiment 1A, Appendix 1, Table VI).

As the sheep in Group II were young, their weight reactions cannot be compared with those of the mature sheep in Groups I and III. In the cases of the latter two groups, it is apparent that the Suffolk-Persian crossbreds decline more rapidly and to a comparatively lower weight level under winter conditions than do Merinos.

It is seen from the results of the oestrous observations (Appendix 4, Tables III, IV, and V), that all three groups of sheep experienced a marked and prolonged anoestrous period. In the case of mature crossbreds the 1933, sexual season may be considered to extend up to the end of July, although two cases of sexual activity occur during August. In the Merinos, the sexual season is 2 to 3 weeks longer. Only 40 per cent. of the young Blackhead Persian-Merino crossbreds exhibited oestrus when from 10 to 12 months of age, and only in one case was more than one dioestrous cycle observed.

The onset of the 1934 sexual season is somewhat earlier in the young crossbred sheep, while in the mature Suffolk-Persian crossbreds the onset of the season is approximately 2 to 3 weeks later than in the Merino sheep.

In general, it may be stated that, in spite of excessive loss of condition or body weight, the sheep continue to exhibit sexual activity until the lowest winter weight is reached. During the anoestrous period, rapid increase in body weight takes place, but the sexual season commences only when a high level weight is attained.

Summaries of the details of the sexual seasons of the three groups are presented in Table I of the text. The mature crossbreds show greater sexual activity than the Merinos during the two portions of the sexual seasons, in that a larger number of dioestrous cycles were experienced by them. The duration of the anoestrous period is longer in Suffolk-Persian crossbreds than in Merinos.

It will be shown in a subsequent experiment (Experiment 6) that Merino flock sheep do not exhibit oestrus at 10 to 12 months of age, and as 40 per cent. of Blackhead Persian-Merino crosses exhibited oestrus at that age, it may be said that these crossbreds are somewhat earlier maturing with respect to sexual activity than Merinos (Table I). However, although the Blackhead Persian is contended to experience continuous annual sexual activity (Part 2 B), the resultant cross of this breed with the Merino experiences a prolonged anoestrous period corresponding to that of Merinos under eastern Transvaal conditions. The Blackhead Persian-Merino crosses show remarkable sexual activity when 22 to 24 months old; during the 1934 sexual season these crossbreds experienced an average of 6·3 dioestrous cycles, whereas mature Suffolk-Blackhead Persians and Merinos experienced an average of 5·6 and 5·2 dioestrous cycles respectively during the same season.

The frequencies of the periodicity of oestrus of the three groups of sheep are given in Table II of the text. Considering the two portions of the sexual seasons of 1933 and 1934, it is seen that, in the case of the Suffolk-Blackhead Persian crosses, the mode of the dioestrous cycles is 16 days, and in 76 per cent. of cases oestrus recurred after 16 and 17 days. In the case of the Bleackhead Persian-Merino crossbreds, the mode is 17 days, and, in 73 per cent. of cases, oestrus recurred after 17 and 18 days. In the case of the Merino sheep, the mode is 18 days, and, in 77 per cent. of cases, oestrus recurred after 17 and 18 days.

It appears from the above, that the genetic influence of the Suffolk in the Suffolk-Merino cross is to lengthen the anoestrous period by about one month and to shorten the duration of the dioestrous cycles. Grant (1934) draws attention to the differences of the duration of the dioestrous cycles in Merinos and in English and Scottish breeds of sheep.

Conclusions.

1. The sexual seasons of Suffolk-Blackhead Persian and Blackhead Persian-Merino crossbred sheep were compared with that of Merino sheep over a period of 12 months.

2. Crossbred sheep react more severely to declining pasture conditions during the autumn and winter months than do Merinos, but the former sheep increase more rapidly in condition during the spring and early summer months than do Merinos.

3. Crossbreds of the types mentioned experience a prolonged anoestrous period during the spring and early summer months under eastern Transvaal conditions; this anoestrum occurs during the same seasons as that evidenced in Merino sheep. Sexual activity persists in spite of declining body weight, and the anoestrous period corresponds to the period during which the greatest increase in body weight occurs.

4. The sexual season of Suffolk-Blackhead Persian crossbreds is 4 to 6 weeks shorter than that of Merinos.

5. The onset of the sexual season of Blackhead Persian-Merino crossbreds occurs approximately one month earlier than that of Merino sheep.

6. Blackhead Persian-Merino crossbreds are more early maturing with respect to sexual activity than Merinos.

7. The mode of the dioestrous cycles in Suffolk-Blackhead Persian crossbreds is 16 days, in Blackhead Persian-Merino crossbreds 17 days, and in Merinos 18 days.

8. The differences in the length of the sexual season, early maturity, and the duration of the dioestrous cycle are considered to be due to genetic factors.

EXPERIMENT 5.

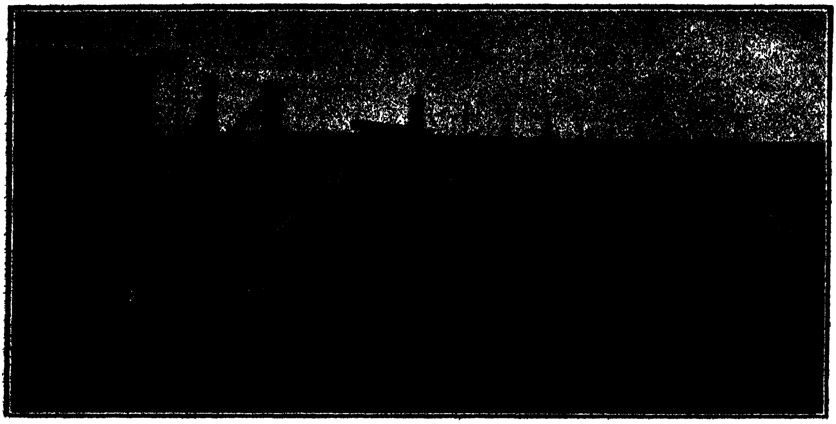


Fig. 22.—Group I: 16.9.33.

Fig. 23.—Group II: 16.9.33.

EXPERIMENT 6.

A. THE AGE OF PUBERTY OF MERINO AND CROSSBRED SHEEP.

The methods of sheep husbandry employed in the eastern districts of the Transvaal have been discussed in the introduction of this thesis. Internal parasites and the low nutritive value of the pastures constitute the greatest problems confronting sheep farmers. The greatest inhibition of growth in sheep occurs during the first twelve months of life. It has been stated that autumn lambing rather than spring lambing has been found by sheepmen to permit better growth in young sheep, as the latter are many months old when worm infection is at its worst during the wet and warm summer months. Yet, many farmers do obtain spring born lambs, the cost of rearing which should be less than the rearing of autumn born lambs, due to the increased amount of feed necessary in the case of the latter. Moreover, the experience of many farmers in the eastern Transvaal is that a large percentage of ewes are more partial to lambing in the spring.

The problems involving the rearing of spring-born lambs under eastern Transvaal conditions have received some attention at the Research Station, Ermelo (Roux and van Rensburg, 1935). At present, it appears that infection with internal parasites, especially tape worm (*Monezia expansa*), overshadows all other problems. The studies on the growth of lambs at the Research Station led to a consideration of the sexual maturity of young sheep.

The earliest age at which ewes can be bred is of considerable economic importance, especially in the case of crossbred (or half-bred) ewes of rapid growing, large framed type, such as the Border Leicester-Merino, which, in a particular system of crossbreeding, may be retained for further crossing. Provided body development results in a satisfactory size, it would be an advantage to breed such sheep as early in life as possible in order to obtain maximum returns by lengthening the life period of reproduction.

The object of the experiment was to determine the age of puberty of Merinos and Border Leicester-Merino crossbreds, and to ascertain the age at which such sheep can be bred under eastern Transvaal conditions of management comparable to those of well managed commercial flocks of the area.

Materials and Methods.—Twenty Merinos and twenty Border Leicester-Merino crossbreds were used in the experiment. These sheep were drafted at random, at the age of 4½ to 5 months, from the ewe lambs bred in connection with crossbreeding experiments conducted at the Research Station during the spring lambing seasons of 1933 and 1934. The following groups, each consisting of 10 sheep, were constructed for the experiment:—

Group I : Border Leicester-Merino Crossbreds, 1933.
Group II : Merinos, 1933.
Group III : Border Leicester-Merino Crossbreds, 1934.
Group IV : Merinos, 1934.

The treatment of the pregnant ewes for the 1933 and 1934 lambings did not vary, although the latter season is considered to have been a somewhat better sheep year. In each case, six weeks prior to lambing, the ewes were given green oat grazing for about two hours daily. A lick of two parts bonemeal and one part salt was self-fed at all times prior to and subsequent to lambing; the lambs had access to the lick.

The Merino and crossbred lambs of each season were run together with their dams in one flock. After weaning, the two types of lambs of each season received identical treatment.

Due to the unsatisfactory growth reflected by the 1933 season lambs, alterations in management were introduced in the case of the following season's lambs. The former lambs were dosed with the Government Wireworm Remedy at three weekly intervals from the age of one month. No supplementary feed apart from oat grazing was given the 1933 season lambs. In December, when the lambs were approximately 2½ months old, they were found to be badly infected with tape worm, and great difficulty was experienced in ridding the sheep of the infection before the end of the summer. When the sheep were about 7 months old, it was considered necessary to supplement the grazing with 4 ounces of maize per sheep per day, the feeding of which was commenced on 30.5.34. In addition, the sheep were put on to green oat grazing for 1 to 2 hours daily from 23.6.34. Small amounts of green veld grazing became available to the sheep during the first week of August, 1934, and, during the latter part of this month, green veld grazing was abundant. Supplementary feeding was discontinued after 15.8.34. During the next winter (1935) supplementary feeding of green oat grazing and 4 ounces of maize was commenced on 7.5.35 and continued up to 17.8.35, when, due to heavy grazing and adverse winter conditions, the sheep had to be removed, kept on dry pasture, and fed 6 ounces of maize per sheep per day.

The 1934 season lambs were dosed for gastric and intestinal worms at 2 and 3 weekly intervals from about 3 weeks of age. Treatment with nicotine and copper sulphate for tape worms as recommended by Mönnig (1932) was tried with only partial success.

When the lambs were approximately two months old, an attempt was made to supplement the veld and green oat grazing with maize, fed by the lamb-creep system. The lambs did not take to such feeding readily and, during the first few months, insignificant quantities of feed were consumed. However, by the time the lambs were weaned, 4 ounces of maize were being fed per sheep. On May 7th, 1935, the sheep were put on to green oat grazing for 1-2 hours daily, and they were fed 4 ounces of maize per sheep per day together with the 1933 season lambs. From that date both seasons' lambs received similar treatment.

All the sheep in this experiment were weighed at birth and at three weekly intervals up to the age of five months; subsequently, weights were recorded less frequently. Up to 2 months of age the lambs were starved for 4 hours before being weighed, but after 2 months they were starved for 12 to 14 hours before being weighed.

All sheep were tested for oestrus daily from the time of weaning, or when they were 4½ to 5 months of age; vasectomised teasers were used for oestrous observations. The sheep were grazed as near the observation yards as possible; the distance to the grazing camps did not exceed half-a-mile.

General farm practices such as inoculation, shearing, and dipping, were followed with these sheep.

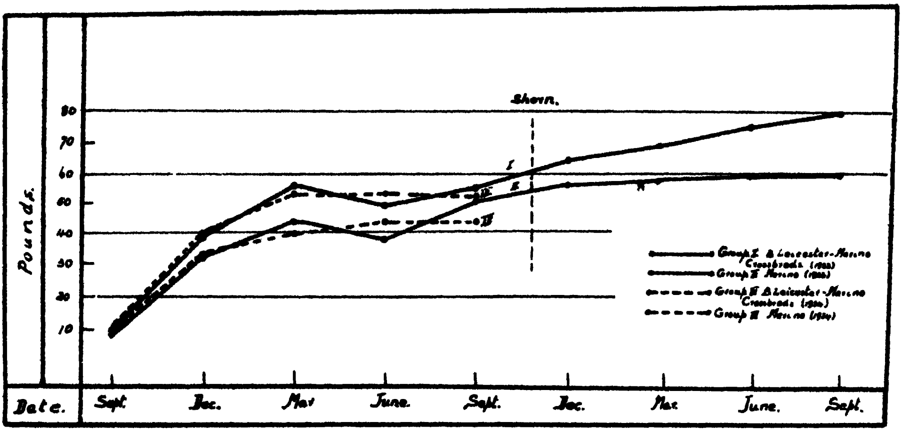
Results.

The birth weights and subsequent weights at three-monthly intervals of Groups I to IV are given in Appendix 5, Tables I to IV.

The accompanying Diagram 5 has been constructed from the mean weights given in the above tables.

DIAGRAM 5.

EXPERIMENT 6.



Mean weights of groups at 3 monthly intervals.

The results of the oestrous observations upon Groups I and II up to September 30th., 1935, are given in Tables I and II of the text.

From the time of the commencement of oestrous observations up to September 30th., 1935, no occurrences of oestrus were observed in Groups III and IV.

Table III has been constructed from Tables I and II to indicate the average of the groups; the frequencies of the periodicity of oestrus have been attached to the table.

It is of interest to note the results of shearing 12 months growth from the 1933 Merinos and crossbreds. The Border Leicester-Merino crossbreds grew staples of 2 to 2¾ inches in length, the wool varied from a 58's to a 64's quality, and the range of variation in the total grease yield was from 1·5 to 3·8 lb., the average being 2·6 lb. In the case of the Merinos, the staple lengths varied from 1¼ to 2 inches, the quality from a 64's to an 80's, and the range of variation of the total grease yield was from 2·8 to 4·7 lb., the average being 3·8 lb. Photographs of the four groups are given in Figs. 24 to 27.

TABLE I.

The Age of Puberty of Crossbred and Merino Sheep.

Group I: Border Leicester-Merino Crossbreds (1933).

Sheep No.	Date of birth.	Age at 1st oestrus.	1935 Occurrences of oestrus.								No. of dioes-trous cycles.	Length of sexual season.	Periodicity of oestrus (days).
			Feb.	March.	April.	May.	June.	July.	August.	Sept.			
		days.										days.	
38320	21.9.33	572	—	—	,16	1, 17	3,	—	—	—	4	49	15 16 17
38321	8.9.33	599	—	—	,30	,16	1, 18	—	—	—	4	50	16 16 17
38342	30.8.33	565	—	,18	,18	5, 21	6,23	—	—	—	6	98	31 17 16 16 16
38374	11.9.33	578	—	—	12, 29	—	3, 21	—	—	—	4	71	17 35 18
38385	14.9.33	556	—	,24	10, 27	13,30	,16	3,	—	—	7	102	17 17 16 17 17 17
38399	17.9.33	560	—	,31	,16	2, 20	6, 22	5,	—	—	7	97	16 16 18 17 16 13
38400	11.9.33	593	—	—	,27	13, 29	—	—	—	—	3	33	16 16
38427	23.9.33	582	—	,28	14, 30	,16	2, 18	4,	—	—	7	99	17 16 16 17 16 16
38430	24.9.33	—	died 5.4.35	—	—	—	—	—	—	—	—	—	—
38436	24.9.33	571	—	—	,18	3, 20	died 27.5.35	—	—	—	3	(incom-plete)	15 17

TABLE II.

Group II: Merino Flock Sheep (1933).

38347	2.9.33	525	9,	,30	,17	5,	11, 30	—	—	—	6	142	49 18 18 37 19
38349	3.9.33	—	—	—	—	—	—	—	—	—	0	—	
38351	1.9.33	—	—	—	—	—	—	—	—	—	0	—	
38361	10.9.33	—	—	—	—	—	—	—	—	—	0	—	
38404	13.9.33	—	—	—	—	—	—	—	—	—	0	—	
38406	11.9.33	620	—	—	—	.24	—	—	—	—	1	1	
38450	25.9.33	—	—	—	—	—	—	—	—	—	0	—	
38469	1.10.33	537	—	,22	8, 25	11, 29	—	—	—	—	5	69	17 17 16 18
38479	5.10.33	492	9,	—	—	—	—	—	—	—	1	1	
38536	17.10.33	—	—	—	—	—	—	—	—	—	0	—	

TABLE III.

The Sexual Activity of Young Crossbred and Merino Sheep.

Group.	Average age at 1st oestrus.	Average No. of dioestrous cycles.	Average length of sexual season.	Frequencies of the periodicity of oestrus (days).										Total.
				13	15	16	17	18	19	31	35	37	49	
	days.		days.											
I........................	575·1 (9)	5·2 (9)	74·9 (8)	1	2	16	13	2	—	1	1	—	—	36
II........................	543·5 (4)	3·2 (4)	53·2 (4)	—	—	1	2	3	1	—	—	1	1	9

NOTE :—The numbers in brackets indicate the number of individuals concerned in the averages.

Discussion.

The growth curves of the four groups of sheep, as illustrated in Diagram 5, indicate an expected higher rate of growth of the Border Leicester-Merino crossbreds (Groups I and III) than that of the Merinos (Groups II and IV).

A decreased rate of growth is evidenced during the period of 3 to 6 months of age. In spite of the supplementary feeding of concentrates to the 1934 lambs, their growth is somewhat less than that of the 1933 lambs, the pasture of which was unsupplemented during that period. It is during December and January that tapeworm infection is most severe and the infection of the 1934 lambs was greater and of longer duration. The adverse effects on growth are most marked up to the age of 12 months. The 1933 and 1934 crossbreds at 6 months of age weighed 57·2 and 54·2 pounds respectively and at 12 months of age only 56·4 and 52·7 pounds respectively. The 1933 and 1934 Merinos at 6 months of age weighed 45·4 and 41·2 pounds respectively and at 12 months of age only 52·0 and 45·4 pounds respectively. Bartel and Johnstone (1934) found that, under Western Province (South Africa) conditions, Border Leicester-Merino crossbreds and Merinos weighed 70·7 and 67·4 pounds respectively at 4·5 months of age. Maré (1930) indicates that Merino (flocks) at the ages of 3 and 6 months, under Karroo (South African) conditions, attain the weights of 46·3 and 59·7 pounds respectively. Colebatch and Scott (1928), under South Australian conditions, found that Border Leicester-Merino crossbreds and Merino lambs reared under farm conditions on natural pasture only, weighed 65·3 and 60·4 pounds respectively at the age of 14 weeks. It is apparent that the weights of the sheep reported upon in this experiment are considerably lower than that of those reported upon by the above authors.

Slight beneficial effects of supplementary feeding are indicated in the results during the period March to June, when the 1933 lambs lost weight while Groups III and IV at least made small gains.

The results of growth and improvement of condition depend greatly upon the time of the arrival of the spring rains. In the case of the 1933 lambs, green grazing was available when the sheep were about 11 months old, but in the case of the 1934 lambs, their first winter was long, dry, and severe, for by the end of September, 1935, no green grazing was available. In cases such as the latter, supplementary feeding, as employed on a large scale in general farm practice, cannot result in a satisfactory rate of growth. It is, therefore, apparent that, in order to obtain a higher rate of growth throughout the first 12 months, a higher level of feeding must be adopted, but it is questionable whether satisfactory results will be obtained unless a more complete check on worm infection is accomplished.

The results of the oestrous observations up to the age of twelve months indicate that, under the conditions to which Groups I to IV were subjected, sexual activity does not occur. Quinlan, Maré, and Roux (1930) found that Merino sheep under Karroo conditions are sexually mature at 9 to 10 months of age. It has been indicated in a previous report (Experiment 5) that 40 per cent. of Blackhead Persian-Merino crossbreds are sexually mature at the ages of 10 to 12 months.

Diagram 5 further indicates that the 1933 lambs made slow progress during the second year, and the Merinos, Group II, merely maintained their weight over a long period. It was, however, during the ages of 12 to 24 months that sexual activity commenced (Tables I and II of the text).

The crossbreds (1933) show an almost uniform increase in weight from 12 to 24 months of age, and sexual activity commenced at about 18 months and terminated at approximately 21 months of age (Table I). At 19 months of age, 90 per cent. of these sheep had attained sexual maturity and the mean weight at about that age was approximately 75 pounds.

Poor increase in weight is shown by the Merinos (1933) during the 12th to the 24th month of age. Although oestrus was observed at an early date in two individuals, only 40 per cent. of the sheep showed oestrus at from 18 to 20 months of age, and, in half these cases, oestrus occurred only once (Table II). The mean weight of the Merinos at this age was approximately 59 pounds.

It is apparent from Tables I and II of the text, that both types of sheep have a restricted sexual season, which commences at the age of about 18-19 months in February or March and terminates in June or a month later.

In the case of the Border Leicester-Merino crossbreds, the age at the exhibition of the first oestrus ranged from 556 to 599 days, the average age being 575·1 days (Tables I and III). The length of the first sexual season of these sheep varies from 33 to 102 days, the average being 74·9 days. During the sexual season, from 3 to 7 dioestrous cycles are experienced and the average number of cycles is 5·2. The duration of the dioestrous cycle varies from 13 to 35 days with a mode of 16 days, and, in approximately 81 per cent. of cases, oestrus recurs after 16 and 17 days.

The information upon the young Merinos is insufficient to permit a comparison of details, although the corresponding data obtained from some of these sheep, Group II, have been included in Table III. There is an indication that the duration of the dioestrous cycle of Merinos is longer than that of the crossbreds.

B. THE SEXUAL ACTIVITY OF YOUNG SHEEP OF VARIOUS BREEDS AND CROSSES UNDER KARROO (CAPE) CONDITIONS.

Oestrous observations upon sexual activity in young sheep of various breeds and crosses are being made by the Research Section of the Sheep and Wool Division at the "Grootfontein", School of Agriculture, Middelburg, Cape. The experiments are under the direction of Dr. Quinlan, Sub-Director of Veterinary Services, Onderstepoort, Pretoria. By the kind permission of Dr. Quinlan, certain of the results of these experiments are presented here in order to indicate the varying degrees of sexual activity exhibited by certain breeds and types of young sheep under Karroo conditions.

The sheep under observation have been run on the veld which has been supplemented with a lick consisting of the following: Salt 8·4 lb., bonemeal 8·4 lb., tobacco dust 1 lb., and sulphur 1 lb. Oestrous observations are made with vasectomised teasers at the observation yards to which the sheep are brought once daily.

Some of the data kindly supplied to the author have been analysed and presented in Table IV of the text.

It is seen that Merino sheep at 16·5 months of age weigh 66·6 pounds. During the ages of 12 to 17·5 months, 50 per cent. of the sheep show oestrus, and great variation exists in the number of dioestrous cycles experienced; the maximum number of cycles experienced is 7. The sheep that exhibit oestrus go into anoestrum during June and July. The mean duration of the inactive period is 140·5 days.

Blackhead Persian sheep at 16·5 months of age weigh 67·8 pounds. All sheep are sexually active during the ages of 12 to 17·5 months and 9 to 11 dioestrous cycles are experienced by these sheep, the average being 9·8 cycles during a period of 169 days. Forty per cent. of the sheep did not show oestrus upon the expected dates during the earlier part of September, which suggests that these sheep might have gone into anoestrum. The mean duration of the inactive period is only 13·1 days.

The Southdown-Blackhead Persian crossbreds weigh only slightly more, 2·7 pounds, at 16·5 months of age than do the Blackhead Persian sheep. All the former sheep are sexually active during the ages of 12 to 17·5 months, but the mean number of dioestrous cycles experienced by the crossbreds is 7·3, or 2·5 less than that of the Blackhead Persian sheep. All the sheep go into anoestrum during July and August. The mean duration of the inactive period is 56·9 days.

The data upon the purebred Ronderibs have not been included as the number is small (6) and the dates of birth vary considerably beyond the usual period of lambing of six weeks. However, it appears that certain individuals of this breed reach sexual maturity at 6·5 months of age and that the age of puberty depends greatly upon the time of birth.

The Welsh Mountain-Ronderib sheep were approximately 7·5 months old when observations were commenced. They experienced an average of five dioestrous cycles during the ages of 7·5 to 12 months. It appears from the oestrous observation records that the first exhibitions of oestrus recorded for all these crossbreds were the first occurences of oestrus of these sheep and, therefore, such crossbreds become sexually mature at approximately 7·5 months of age. The sexual activity of these sheep ceases in June and July and the mean duration of the inactive period is 101·1 days. Such crossbreds grow rapidly; they attain 67·1 pounds at the age of 11 months.

TABLE IV.

The Sexual Activity of Various Breeds and Crosses of Sheep under Karroo Conditions.

Breed or type.	No. of sheep under observation.	Duration of observation period: Apr. 1st. to Sept. 16th, 1935.	Average age at commencement of observations.	Mean weight.	Maximum number of sexually active sheep.	Number of dioestrous cycles.													Mean duration of inactive period.*
						Total.	Frequencies.												
							0.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	
		(Days.)	(Months.)	(lb.)															(Days.)
Merino.............	10	169	11·5	66·6 at 16·5 months	5	20	5	1	1	1	—	1	—	1	—	—	—	—	140·5
Blackhead Persian....	10	169	11·5	67·8 at 16·5 months	10	98	—	—	—	—	—	—	—	—	—	5	2	3	13·1
Southdown-Blackhead Persian	10	169	11·5	70·5 at 16·5 months	10	73	—	—	—	—	—	—	3	3	2	2	—	—	56·9
Welsh Mountain-Ronderib	10	169	7·5	67·1 at 11·0 months	10	50	—	—	—	1	2	4	2	1	—	—	—	—	101·1

* NOTE.—In the case of the mean duration of the inactive period, cases in which inactivity existed between the time of the commencement of observations and the onset of oestrus, this period of inactivity has been added to the period of inactivity prior to the date up to which the observations have been considered, that is up to September 16th, 1935.

Conclusions.

1. Observations were made to ascertain the age of sexual maturity of Border Leicester-Merino crossbreds and Merino flock sheep under eastern Transvaal conditions of management.

2. Continuous growth is inhibited in crossbreds and Merinos during the first 12 months. Worm infection is largely responsible for the inhibition of the progress of growth during the ages of 3 to 6 months. A higher level of feeding than that generally practised during the winter months is essential in order to promote continuous growth.

3. Border Leicester-Merino crossbreds at the age of 19 months weigh approximately 75 pounds; at this age 90 per cent. attain sexual maturity and experience a number of normal dioestrous cycles.

4. Merino flock sheep at the age of 19 months weigh approximately 59 pounds; at this age 40 per cent. attain sexual maturity, but a number of normal dioestrous cycles is experienced in only 20 per cent. of cases.

5. Border Leicester-Merino crossbreds and Merino flock sheep at the ages of from 17 to 21 months, experience a restricted sexual season of about 50 to 75 days duration.

6. Border Leicester-Merino crossbreds attain satisfactory size to permit breeding at 19 months of age, and the regular occurrence of oestrus permits mating these sheep at that age.

Spring born Merino sheep are small and immature at the age of 19 months under eastern Transvaal farm conditions and mating at that age is not recommended.

7. The sexual activity of young sheep of the following breeds and crosses under Karroo conditions has been analysed: Merino, Blackhead Persian, Southdown-Blackhead Persian, Ronderib, and Welsh Mountain-Ronderib.

(*a*) All the breeds and crosses exhibit sexual activity during the months of April to September, but, in certain of these types, sexual activity is not extended throughout the entire period.

(*b*) The lowest sexual activity is reflected by Merinos 12 to 17·5 months old; 50 per cent. of the sheep are sexually active and the active sheep go into anoestrum during June and July.

(*c*) The highest degree of sexual activity is experienced by the Blackhead Persian sheep, 100 per cent. of which are sexually active and experience regular dioestrous cycles during the ages of 12 to 17·5 months.

(*d*) Although a high degree of sexual activity is experienced by Southdown-Blackhead Persian crossbreds between the ages of 12 to 17·5 months, these sheep go into anoestrum during July and August. The reduced period of activity is considered to be due to the genetic influence of the Southdown.

(*e*) Ronderib lambs become sexually active at approximately 6 months of age; the majority of young sheep go into anoestrum during May to August.

(*f*) Welsh Mountain-Ronderib crossbreds become sexually active at approximately 6 months of age, but these sheep go into anoestrum during June and July.

8. Merino sheep are better grown and at least 50 per cent. experience sexual activity at an earlier age under Karroo veld conditions than under eastern Transvaal conditions.

EXPERIMENT 6.

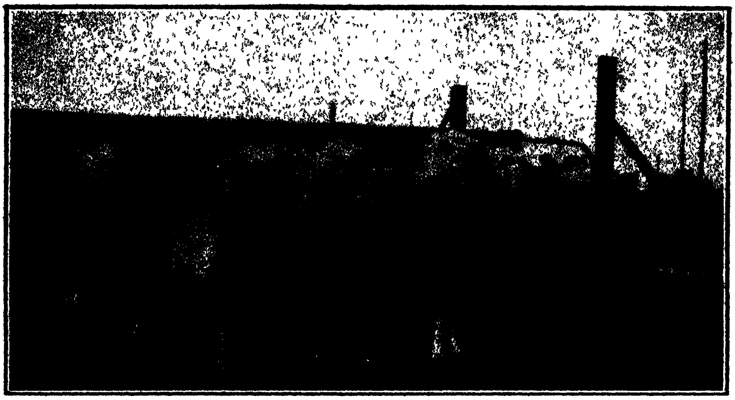


Fig. 24.—Group 1: 23.7.35.

Fig. 25.—Group II: 23.7.35.

EXPERIMENT 6.

Fig. 26.—Group III: 23.7.35.

Fig. 27.—Group IV: 23.7.35.

EXPERIMENT 7.

THE INFLUENCE OF CLIMATE UPON THE SEXUAL ACTIVITY OF YOUNG MERINO EWES.

Farmers in the Transvaal frequently purchase sheep from Karroo breeders. The reactions of sheep to altered conditions of climate are of practical interest; it is suspected that upon transfer temporary sexual inactivity results. Quinlan and Maré (1931) consider that such inactivity is experienced when sheep are transferred from the humid coastal districts to the arid climate of the Karroo. Merino sheep under Karroo conditions exhibit continuous annual sexual activity (Quinlan and Maré, 1931), but it has been indicated by the results of preceding experiments reported in this thesis that such activity is restricted under the conditions obtaining at the Research Station, Ermelo. It has not been determined whether these differences in the degree of polyoestrum are due to climatic, nutritional, or other factors.

The physiographical conditions of the Karroo differ from those of the eastern Transvaal highveld. The former conditions are considered to be infinitely more favourable for sheep farming than those of the latter area. The greatest advantage of the Karroo is generally accepted to be the comparatively higher nutritive value of the natural pasture, which, in addition, is not subject to drastic reductions in nutritive value during the dry winter months. In Karroo areas, sheep experience marked loss of weight only during prolonged droughts. With respect to climate, the Karroo and eastern Transvaal highveld are both summer rainfall areas, but the former is semi-arid while the annual rainfall of the latter approximates 30 inches; extreme temperatures are experienced in both areas. The following Table I gives certain meteorological data recorded at the Grootfontein School of Agriculture, Middelburg, Cape, and this data may be compared with the corresponding data recorded at the Government Forest Nursery which adjoins the Research Station, Ermelo (Introduction, Table I).

TABLE I.

Meteorological Records: Grootfontein, School of Agriculture, Middelburg, C.P.

Month 1935.	Total Rainfall.	Highest Maximum.	Lowest Maximum.	H. (Screen) Minimum.	L. (Screen) Minimum.
January..........	1·15	94·8	72·9	63·2	39·5
February.........	2·83	90·8	62·4	65·0	37·3
March............	2·30	88·5	62·1	60·8	35·2
April............	1·73	80·6	56·8	55·3	29·6
May.............	2·66	68·7	44·4	55·0	25·8
June.............	0·99	66·0	41·5	44·7	22·5
July.............	0·53	68·0	35·0	43·0	19·1
August...........	0·26	74·5	39·6	40·7	16·0
September........	0·76	83·8	53·2	46·0	27·0
October..........	0·34	91·3	64·4	64·9	28·7

The objects of this experiment were to determine the reaction, with respect to sexual activity, of young Merino ewes which are transferred from the Karroo to the eastern Transvaal, and to ascertain whether any reaction that may result is due to altered climatic conditions or to nutritional factors.

(NOTE: The experiment has been planned to permit the extension of the observations in order to determine the following:—

1. The influence of climate upon the rhythm of the sexual cycle when sheep are:
   - (i) Mated in the spring to lamb in the autumn under:
     - (*a*) Eastern Transvaal conditions.
     - (*b*) Karroo conditions.
   - (ii) Mated in the autumn to lamb in the spring under:
     - (*a*) Eastern Transvaal conditions.
     - (*b*) Karroo conditions.
   - (iii) Not mated under:
     - (*a*) Eastern Transvaal conditions.
     - (*b*) Karroo conditions.
2. The influence of climatic and nutritional factors when such sheep are not mated under:
   - (*a*) Eastern Transvaal conditions.
   - (*b*) Karroo conditions.

It will be noticed that the experiment has been commenced comparatively recently, March, 1935; consequently, the results of this latter phase of the experiment are not available for the present report, but they will appear in a later issue of the Onderstepoort Journal).

Materials and Methods.—Eighty Merino ewes, bred from the large flock maintained by the "Grootfontein," School of Agriculture, Middelburg, Cape, were drafted into the experiment in March, 1935, when the sheep were approximately 10·5 months of age. Forty of the sheep were transferred to the Research Station, Ermelo, where they arrived on 16.3.35. Oestrous observations were commenced the following day and after four days, the sheep were divided into four groups. The remaining 40 sheep were retained at the "Grootfontein," School of Agriculture. Due to a delay, the oestrous observations at the latter Institution were commenced about 14 days later than those at Ermelo.

Observations at each of the two centres were conducted on four groups each consisting of 10 sheep. Oestrous observations upon 10 of the sheep included in the number at the "Grootfontein School of Agriculture" (Group V) were conducted in connection with studies on sex physiology of sheep under the direction of Dr. Quinlan, Sub-Director of Veterinary Services, Onderstepoort, Pretoria. Dr. Quinlan has kindly consented that the results obtained from this veld group, be used for comparative purposes in this experiment.

The eight groups were given the following treatments:—

A. *Ermelo:*

Group I: On veld supplemented by a lick; supplementary feeding during the winter months.

Group II: Dry-lot: Maize 6 oz., lucerne hay 1·5-2 lb. and a lick.

Group III: Similar to that of Group II.

Group IV: Similar to that of Group II.

B. *Grootfontein:*

Group V: On veld supplemented by a lick.

Group VI: Similar to that of Group II.

Group VII: Similar to that of Group II.

Group VIII: Similar to that of Group II.

(NOTE.—The veld sheep, Groups I and V will not be bred. Another of the remaining groups at each of the centres will not be bred. A group at each of the centres will be bred from November 15th, 1935, to produce autumn lambs, while the remaining group at each centre will be bred from April 15th, 1936, to produce spring lambs. Continued observations upon the sexual activity should reveal any differences at the two centres that may be reflected by sheep which are not bred and those that are bred at different seasons of the year.)

The rations of Groups II to IV and VI to VIII were similar. In both sections A and B, yellow maize, lucerne hay, and a lick consisting of 3 parts bonemeal and 1 part of salt (by weight), were fed. Unfortunately, it has not been possible to utilize feeds from the same source of supply; however, the maize used at both centres was Transvaal or Free State grown and the lucerne was Karroo grown.

The above dry-lot fed groups were kept in small yards devoid of grazing and in which all rations were fed. It has been reported that, unfortunately, the quality of the lucerne hay fed to Groups VI, VII, and VIII at "Grootfontein" was not uniformly of good quality; reference to this point will be made in the subsequent discussions.

The daily oestrous observations at both centres were conducted between 7 and 8 a.m., vasectomised teasers being used. At the close of the sexual season, 1935, oestrous observations at the Research Station, Ermelo, were made twice daily for three months in order to ascertain whether cases of oestrous periods of abnormally short duration occurred in young Merino ewes. No such cases were revealed.

The sheep at the Research Station, Ermelo, were weighed at 14 day intervals, while those at the "Grootfontein", School of Agriculture, were weighed at 28 day intervals. It will be noticed that the commencement of recording weight data of the veld group at the latter Institution was delayed. All sheep were starved for 12 to 14 hours before being weighed.

The sheep were dosed with Government Wireworm Remedy at 28-day intervals. Inoculation against bluetongue and the annual shearing took place at approximately the same date at the two institutions.

In the case of Group I at the Research Station, Ermelo, it was intended to supplement the winter grazing with green oat grazing by permitting the latter for 1 to 2 hours daily. Due to the prolonged absence of rain and the severity of the winter, green cereal grazing could not be supplied throughout the winter months and supplementary feeding of maize had to be undertaken. The total period during which supplementary green oat grazing was allowed was approximately three months, while the period during which 4 to 6 ounces of maize were fed was approximately two months.

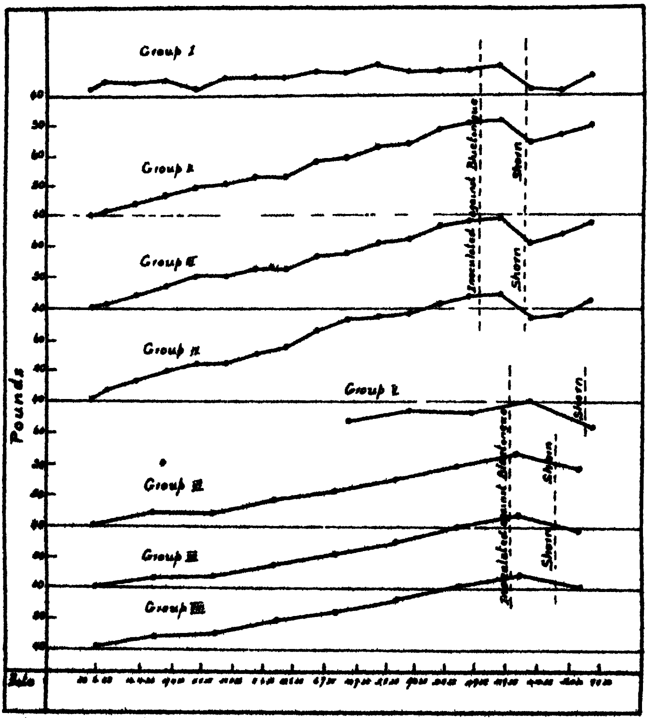
As the veld groups at both centres were run together with other experimental sheep, the lick consumption of the sheep in this experiment was taken as the average of the entire flock.

Results.

The weight data of Groups I to VIII are given in Appendix 6, Tables I to VIII; the mean weights at each interval have been computed and from these Diagram 6 has been constructed.

DIAGRAM 6.

EXPERIMENT 7.



Mean weights of groups at 14 and 28 day intervals.

An analysis of the mean weights of the groups and the shearing data are presented in Table II.

TABLE 11.

Mean Weight and Shearing Data.

Group.	Mean initial weight.		Mean weight prior to shearing.		Percentage gain per 100 days on mean initial weight.	Shearing data. Grease wool yields.		Mean weight immediately after shearing.	
						Range.	Average.		
	lb.	Date.	lb.	Date.	Per cent.	lb.	lb.	lb.	Date.
I.	42·0	23.3.35	46·8	28.9.35	6·0	5·8– 7·2	6·3	39·6	12.10.35
II.	41·5	,,	69·0	,,	34·9	6·9– 9·7	8·8	61·4	,,
III.	41·8	,,	67·8	,,	32·9	6·4– 9·8	8·4	60·0	,,
IV.	41·9	,,	73·3	,,	39·6	7·9–11·0	8·9	65·6	,,
V.	(41·5)*	(25.3.35)	69·0	23.10.35	31·1	7·4–10·2	8·6	60·1	7.11.35
VI.	41·2	25.3.35	61·6	7.10.35	25·1	5·5–10·3	7·9	56·8	4.11.35
VII.	41·2	,,	62·1	,,	25·7	6·3– 9·8	7·9	56·8	,,
VIII.	41·2	,,	63·3	,,	27·2	6·4–10·6	8·2	58·8	,,

* NOTE.—In the case of Group V no initial weight was recorded. The mean weight given has been computed from the mean initial weights of all other groups.

TABLE III.

A Summary of Sexual Activity.

Group.	Period of oestrous observations.		No. of sexually active sheep.	No. of dioestrous cycles.									Months during which sexual activity occurred.
				Frequencies.								Total.	
				0.	1.	2.	3.	4.	5.	6.	7.		
	Date.	Days.											
I.	17.3.35–15.11.35	244	0	10	—	—	—	-	—	—	—	0	No activity.
II.	” ”	”	2	8	1	—	1	—	—	—	—	4	May, June, October.
III.	” ”	”	2	8	2	—	—	—	—	—	—	2	May, October.
IV.	” ”	”	3	7	2	1	—	—	—	—	—	4	May, June.
V.	1.4.35–15.11.35	229	5	5	1	—	1	1	1	—	1	20	April, May, June, July.
VI.	8.4.34– ”	222	2	8	1	—	—	1	—	—	—	5	June, July, August.
VII.	” ”	”	4	6	—	2	1	—	1	—	—	12	April, May, June, July.
VIII.	” ”	”	2	8	—	1	1	—	—	—	—	5	May, June, July.

The details of the results of the oestrous observations on Groups I to VIII are given in Appendix 6, Tables IX to XVI.

A summary of the sexual activity of the groups is given in Table III of the text.

The feed and lick consumption of the eight groups of sheep are given in Table IV of the text.

TABLE IV.

Feed and Lick Consumption.—Average per Sheep per Day.

Group.	Maize.	Lucerne hay.	Lick (bone meal and salt.
	oz.	oz.	oz.
I.................	Control	On pasture	·537
II.................	6·0	30·4	·026
III.................	6·0	30·4	·026
IV.................	6·0	30·4	·026
V.................	Control	On pasture	·210
VI.................	4·5	23·6	·017
VII.................	4·4	24·7	·018
VIII.................	3·7	24·8	·017

Photographs of each of the eight groups of sheep are given in Figs. 28 to 35.

Discussion.

Quinlan, Maré, and Roux (1930) reported that Merino ewes transferred from the Karroo (Middelburg, Cape) to the Onderstepoort Laboratory, Pretoria, Transvaal, at the age of 6 to 8 months, all showed oestrus during the month of January (1928) when they were 9 to 10 months old. It is stated that " . . . this is generally what is expected under South African conditions; lambs born in the autumn and early winter, show oestrus the following summer at the age of 9 to 10 months if maintained in good condition ". Quinlan and Maré (1931) reported that, under favourable Karroo conditions, non-pregnant and non-lactating ewes experience a continuous series of dioestrous cycles throughout the year.

It was considered that the sheep chosen for this experiment, being approximately 10·5 months of age, would be sexually mature and that they would, under Karroo conditions, be exhibiting normal ovarian activity. However, the detailed results of the oestrous observations indicate that in only 3 out of 80 cases did oestrus occur within 20 days after the commencement of the observations; all 3 of the cases of sheep which exhibited an early oestrus were individuals which had not been transferred to Ermelo. (Appendix 6, Tables IX to XVI.) Further, it is seen from these tables that 75 per cent. of the ewes revealed no sexual activity during the period of observations of about 8 months, or when the sheep were between the ages of 10·5 and 18·5 months.

Diagram 6 illustrates the weight tendencies of the eight groups of sheep. With the exception of Group I, the veld group at Ermelo, the groups showed almost constant increases in weight and the mean weights of these groups just prior to and immediately after shearing compare very favourably with those of a similar type of sheep reported upon by Quinlan, Maré, and Roux (1930). It is seen that, in spite of Group I being given what was considered good farm management, this group maintained a mean weight at approximately the 45 lb. level. As Groups II to VIII attained weights just prior to shearing ranging between 62 and 73 lb., the weight of Group I must be considered as unsatisfactory.

The extent of gain accomplished by each of the groups and other data relative to body weight and wool production, are given in Table II. Further evidence of the unsatisfactory reaction of Group I is revealed, as the percentage gain on the initial weight up to just prior to shearing is only 6·0 per cent. per 100 days, whereas that of all other groups exceeds 25 per cent. The mean weight of Group I immediately after shearing is only 39·6 lb., whereas that of other groups approximates 60 lb. The average grease wool yield of the former is 6·3 lb., which is significantly less than that of the latter groups, although it may be said that, considering the apparent inhibition of body growth of Group I, the wool yields are surprisingly high.

The dry-lot fed sheep at Ermelo, Groups II, III, and IV, are seen to have made higher gains than the corresponding sheep, Groups VI, VII, and VIII, at "Grootfontein" (Table II). The percentage gains per 100 days up to the time of shearing of the Ermelo sheep are 34·9, 32·9, and 39·6, whereas the corresponding gains of the Grootfontein sheep are 25·1, 25·7 and 27·2 per cent. The mean weights of the three dry-lot fed groups after shearing are somewhat higher at the former centre, and the same remark may be applied to the wool yields. This difference is suspected to be due to the smaller amounts of feeds consumed by the three groups at "Grootfontein" (Table IV). Previous mention was made of the difference in quality of lucerne hay fed to the sheep at "Grootfontein"; this appears to be the main factor involved.

The dry-lot fed groups at Ermelo compare very favourably with the veld group at Grootfontein with respect to weight and wool production; in the latter the mean wool yield is 8·6 lb. and the mean body weight after shearing is 60·1 lb.

It is seen from Table III that the group on veld at Ermelo is the only group in which no sexual activity was experienced. On the other hand, the veld Group V, under Karroo conditions, showed greatest sexual activity; 50 per cent of the sheep exhibited oestrus, one sheep experienced as many as 7 dioestrous cycles, and the total number of cycles of the group is seen to be 20; sexual activity occurred during the months of April to Jul.y

As the three groups of dry-lot fed sheep at each of the two centres received identical treatment during the period under consideration, for the present the sexual activity of the 30 sheep at

Ermelo may be compared with that of the 30 sheep at " Grootfontein ". At the former centre, 7 sheep showed oestrus, at the latter 8 sheep, but the total number of dioestrous cycles experienced by these sheep is seen to be 10 and 22 respectively (Table III). At Ermelo, the majority of active sheep experienced only one dioestrous cycle, the maximum number of cycles being 3; at " Grootfontein," the majority of active sheep experienced 2 and 3 dioestrous cycles, the maximum number of cycles being 5. It should be pointed out that one sheep in each of Groups II and III exhibited oestrus during October; no previous activity had been observed in these sheep, and no instances of activity during September, October, and November were observed at " Grootfontein ". (Appendix 6, Tables IX to XVI.) Apart from these two instances of activity at Ermelo, the remaining limited activity appears to have been restricted to May and June, while at " Grootfontein " sexual activity occurred in all the months from April to August.

With the exception of two cases in Group V and one case in Group VII, the onset of sexual activity may be considered to have commenced after oestrous observations had begun. It appears, therefore, that these sheep experienced a restricted season of sexual activity (Appendix 6, Tables IX to XVI).

By consulting the details of the oestrous observations and the individual weight data (Appendix 6, Tables I to XVI), it will be found that most of the sheep at both centres which experienced sexual activity are below the average weight of their respective groups and, in fact, in many cases they are some of the lightest sheep.

Conclusions.

1. Observations were made to determine the effects of transferring 40 autumn-born Merino ewes at the age of 10·5 months from the Karroo to the eastern Transvaal.

The observations are reported up to the time when the sheep were 18·5 months of age.

It is indicated that the plan of the experiment eventually aims to ascertain the influence of the absence of breeding and the time or season of breeding upon ovarian activity and the rhythm of the sexual seasons.

2. Merino ewes under Karroo veld conditions up to the age of 18·5 months, attain a weight of 60·1 lb. off shears, and they yield an average grease wool weight of 8·6 lb. Fifty per cent. of such sheep are sexually active when from 12 to 13½ months old. Sexual activity is restricted to the months of April to July, during which period 7 dioestrous cycles may be experienced, From July up to at least the middle of November, such sheep are in anoestrum.

3. Merino ewes reared under Karroo veld conditions up to the age of 10·5 months and then transferred to eastern Transvaal farm conditions, suffer great inhibition of body growth. They maintain an almost constant weight for 7 months and weigh 39·6 lb. off-shears at the age of 18·5 months. The grease wool production of such sheep is 6·3 lb.

No sexual activity is experienced by such sheep up to the age of 18·5 months.

Nutritional factors are responsible for these adverse effects.

4. Very satisfactory body growth and wool production result when Merino ewes 10·5 to 18·5 months of age are fed a daily ration of 4 to 6 ounces of maize, 1·5 to 2·0 lb. of lucerne hay and a lick of bone meal and salt. Average off-shear weights of 56·8 to 65·6 lb. are attained at the age of 18·5 months, and the grease wool yields of such sheep range from 7·9 to 8·9 lb. Twenty-three to twenty-seven per cent. of such sheep are sexually active when from 12 to 17 months old, but in the majority of cases only 1, 2, and 3 dioestrous cycles are experienced, the greatest activity occurring during May, June, and July. While a few cases of a single oestrus may occur after July, the majority of the sheep are in anoestrum for at least 2·5 months.

An alteration of climate appears to have some effect upon the duration of the sexual season; a change from the Karroo to the eastern Transvaal reduces the number of dioestrous cycles experienced by approximately 54 per cent.

EXPERIMENT 7.

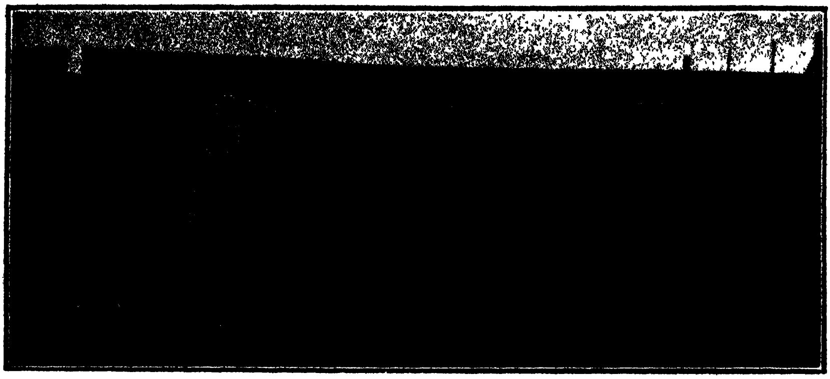


Fig. 28.—Group I: 23.7.35.

Fig. 29.—Group II: 23.7.35.

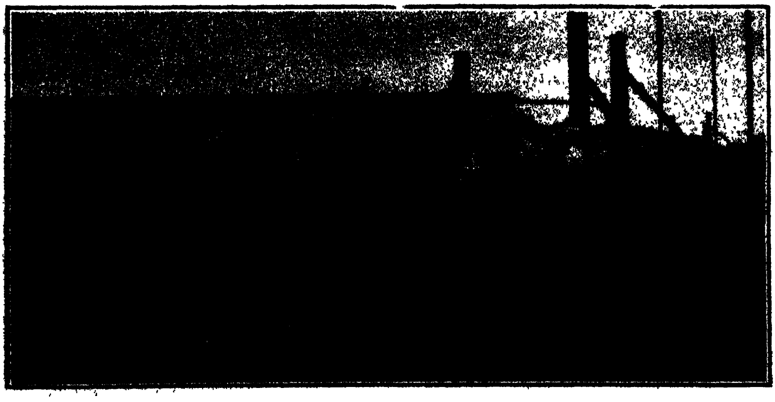


Fig. 30.—Group III: 23.7.35.

EXPERIMENT 7.

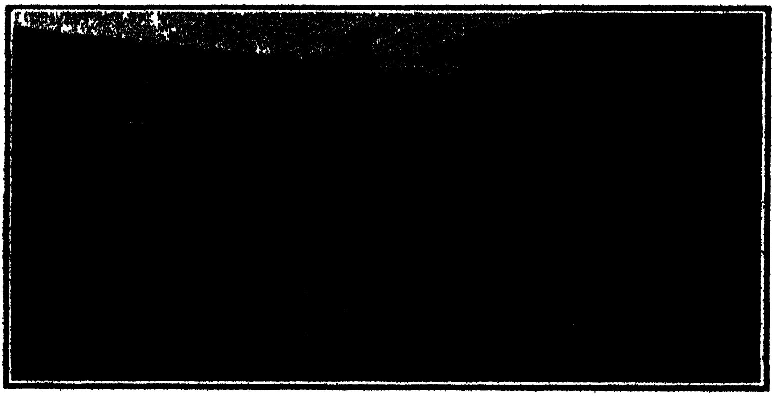


Fig. 31.—Group IV· 23.7.35.

Fig. 32.—Group V: 23.7.35.

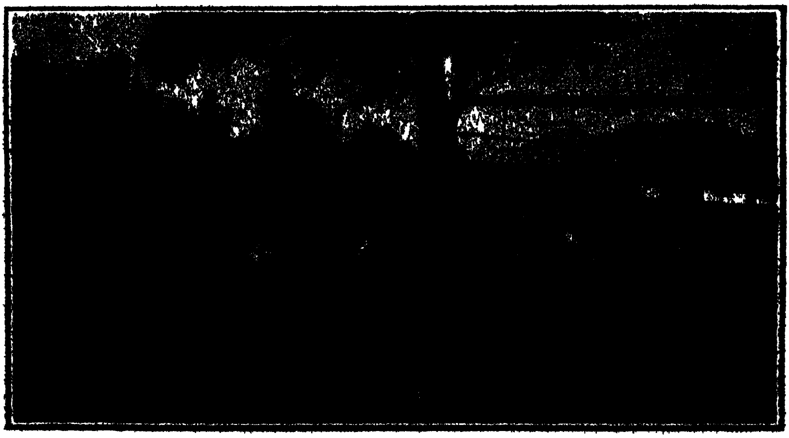


Fig. 33.—Group VI: 23.7.35.

Experiment 7.

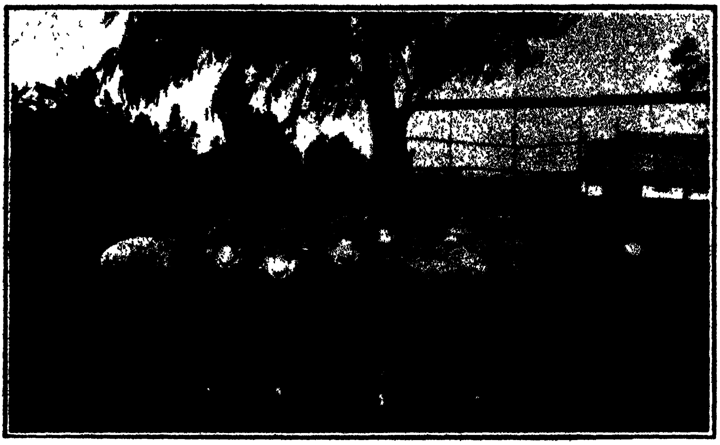


Fig. 34.—Group VII: 23.7.35.

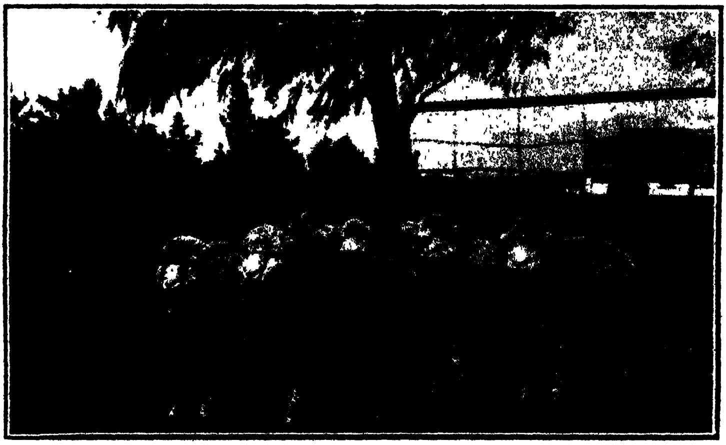


Fig. 35.—Group VIII: 23.7.35.

EXPERIMENT 8.

THE EFFECTS OF INOCULATION, SHEARING, AND DIPPING UPON SEXUAL ACTIVITY.

In most areas in South Africa, inoculation against bluetongue and dipping against external parasites are essential practices. Generally, inoculation is done about three weeks before shearing, which is followed by dipping. The usual custom is to complete these farm operations before the mating season which, when autumn lambs are obtained, falls during October, November, and December, or even until as late as January. Variations of the order of inoculation, shearing, dipping, and mating do occur, for, in some areas, shearing is undertaken later and even as late as February. It is not necessary here to enter into the pros and cons of the best procedure for any particular area. It is evident that less difficulty in regulating the practices must be experienced when mating is done during the autumn than when spring mating is undertaken.

Frequently, suspicion exists that inoculation, shearing, and dipping affect the sexual activity of ewes in that either the onset of the sexual season is delayed, or the continuity of the dioestrous cycles is interrupted. Apart from making observations to prove or disprove these beliefs, it appeared that any information relative to this aspect would serve to render the findings in all other experiments reported here more complete.

The object of the experiment was to ascertain whether the oestrous cycle in the ewe is affected in any way by inoculation, shearing, and dipping.

Materials and Methods.—Six groups of sheep, each consisting of 10 well-grown mature Merino ewes, were drafted into the experiment on October 13th, 1933. These sheep had been inoculated against bluetongue, shorn, and dipped a year previous to their inclusion in the experiment. It is not known whether all the sheep were bred the previous season.

The sixty sheep were grazed in one flock on natural pasture and they were given a constant supply of a lick consisting of two parts of bone meal and one part of salt. Dosing for gastric and intestinal worms was carried out at 28-day intervals.

The flock was brought to the observations yards once daily for oestrous observations for which vasectomised teasers were used; the sheep were tested in groups of 10-15.

The sheep were weighed at 14-day intervals; they were starved for 12 to 14 hours before being weighed.

The treatments of the groups are given in Table I.

TABLE I.

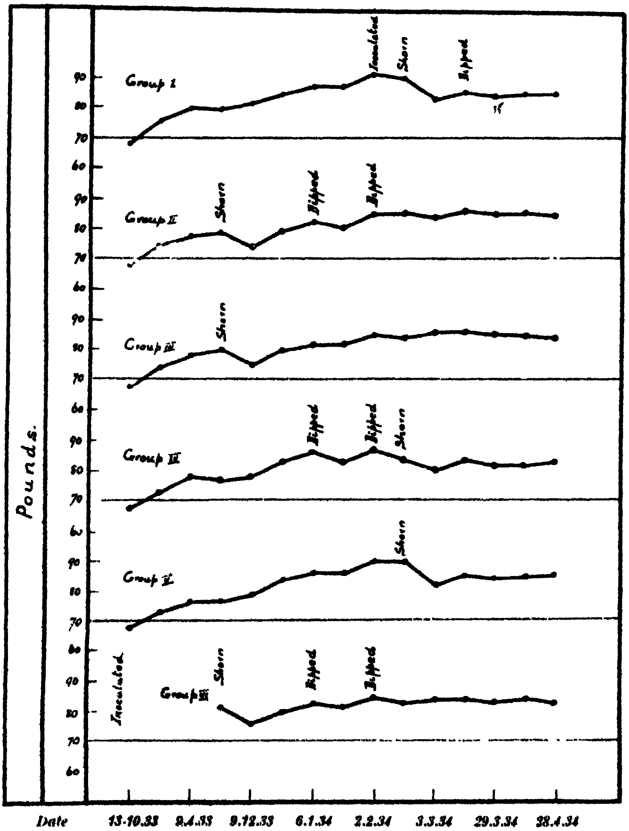
Group.	Inoculation.	Shearing.	Dipping.
I................	February......	February......	March.
II................	No	November.....	January and February.
III................	No	November.....	No.
IV................	No	February......	January and February.
V................	No	February......	No.
VI................	October.......	November.....	January and February.

Results.

The weight data of Groups I to VI are given in Appendix 7, Tables I to VI; the average weights at each period of 14 days have been computed and from these the accompanying Diagram 7 has been constructed.

DIAGRAM 7.

EXPERIMENT 8.



Mean weights of groups at 14 day intervals.

The results of the oestrous observations during the experimental period of 200 days are given in Appendix 7, Tables VII to XII, in which the various treatments to which the groups were subjected have been included; the interoestrous periods of individual sheep are given in these tables.

Tables II and III of the text have been constructed from Tables VII to XII of Appendix 7 in order to present the main features of sexual activity of each group. In Table II the total period has been divided into six periods, the time of application of the treatments forming a basis for such divisions.

It will be noticed that one sheep in Group I, two sheep in Group II, and two sheep in Group III, did not exhibit oestrus during the experimental period. Three sheep in Groups I and II showed oestrus after an extension of the period of testing; in these cases the inactive period is given in brackets (Appendix 7, Tables VII and VIII). The two inactive sheep in Group III were slaughtered for the examination of their ovaries after inactive periods of 307 and 253 days. The results of the examinations of the ovaries of these sheep are given in Appendix 7A and Table IV of the text presents a summary of the findings.

Discussion.

Generally, it is not considered that sheep experience a marked setback in condition from the annual operations of inoculation against bluetongue, shearing, and dipping, but in farm practice these operations are arranged not to take place shortly before or during the mating period as it is suspected that the coming on of heat of ewes is disturbed or inhibited by such treatments.

As shearing generally takes place after the first spring rains and when fresh pasture is available, it may be expected that sheep shorn in the spring or early summer show a sudden increase in weight. It is seen from Diagram 6 that Groups II, III, and VI regained their pre-shearing weights in from 2 to 3 weeks after shearing. However, when shearing is postponed for approximately 3 months, as in Groups I, IV, and V, rapid increases in weight are also experienced during the spring and summer months. It is apparent that, when shearing takes place at the end of summer, no rapid regain of weight takes place. At the end of the experimental period, there is no significant difference between the mean weights of all groups.

When sheep are inoculated against bluetongue annually, the reaction is mild and symptoms of the fever may be seen in only a very small percentage during the 7th to the 15th day after inoculation. An insignificant temporary drop in weight after inoculation is seen in the case of Group I (Diagram 7).

The effect of dipping upon weight is insignificant and this is the case even with sheep in long wool as in Group IV (Diagram 7).

TABLE III.

The Inactive Period and Periodicity of Oestrus.

Group.	Period of testing for oestrus. (days)	Duration of inactive period (days)*		Periodicity of oestrus (days).																				
		Range.	Average	15	16	17	18	19	20	26	31	32	33	34	35	36	37	39	40	41	51	54	69	Total.
I......	200	49–168 (±)	97·6	1	9	25	11	3	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	50
II......	200	83–150 (±±)	109·6	1	8	12	2	—	—	—	—	—	1	1	—	1	—	—	—	—	1	—	1	28
III.....	200	50–151 (±±)	92·8	—	7	19	13	3	1	—	—	—	—	1	1	—	—	—	—	—	—	—	—	45
IV.....	200	0–172	106·9	—	6	22	10	2	—	—	—	—	1	—	2	—	—	—	—	—	—	1	—	44
V......	200	0–190	91·5	1	8	19	11	6	1	—	1	—	—	1	—	—	1	—	1	—	—	—	—	50
VI.....	200	70–161	108·2	—	2	19	8	2	—	1	—	1	—	1	—	2	—	1	—	1	—	—	—	38
Total...	—	—	—	3	40	116	55	16	3	1	1	1	2	4	3	3	1	1	1	1	1	1	1	255

*NOTE :—One sheep in Group I and 2 sheep in Groups II and III did not show oestrus during the experimental period ; these cases have been omitted in the computations of the duration of the inactive period.)

TABLE IV.

The Examination of Ovaries of Inactive Sheep.

Sheep No.	Age.	Con-dition.	Weight.	Total period of testing.	Ovaries.				Graafian follicles.			Corpora lutea.	
					Left.		Right.		No. observed.				
					Weight.	Size.	Weight.	Size.	Left Ovary.	Right Ovary.	Largest	I.	II.
	years		lb.	days.	gm.	cm.	gm.	cm.			cm.	cm.	cm.
35645	6	Fair	81·0	307	0·55	1·5×0·9×0·7	0·81	1·6×1·1×0·9	2	7	0·5	0	0
35965	6	Fair	75·0	253	0·66	1·3×1·0×0·6	0·61	1·3×1·0×0·6	6	3	0·4	0·9×0·7	0·6×0·6

A close study of the results of the oestrous observations in Appendix 7, Tables VII to XII, will indicate that great difficulty is confronted in making an analysis for the interpretation of the results; this is due to marked individual differences of the time of the onset of the sexual season and the number of dioestrous cycles experienced during the period of observation, October, 1933, to April, 1934. Great individual variation has been seen to occur in all other experiments in which oestrous observations were extended over a long period of time. Out of the 60 sheep in this experiment, in only 3 cases did oestrus occur with great regularity; in 5 cases no oestrus was observed during 200 days of the experiment, although in 3 of the 5 cases, oestrus was observed after 208 to 240 days. Again, while in Groups IV and V the maximum number of dioestrous cycles, namely 10 and 12, was experiencmed by individuals, other individuals of the same groups experienced only 1, 2, or 3 dioestrous cycles during the same period. Due to the likelihood of such great variations, greater reliability of results would be obtained by increasing the numbers of sheep in each of the groups to 30. However, the results are of interest in that they may act as a guide to further investigation.

From Table II of the text it is seen that the sheep in Groups II and VI were least active; 36 and 48 dioestrous cycles respectively were experienced in these groups. Both groups were shorn during the spring or before the onset of the sexual season, and Group VI was inoculated prior to shearing. However, Group III was shorn at that time, and, while the activity exhibited by this group is greater than that of the former groups, 53 dioestrous cycles having been experienced, it is less than that of the unshorn groups in which from 54 to 60 dioestrous cycles were observed. The greater amount of sexual activity exhibited by the three groups which were not shorn during November, is due, in the cases of Groups IV and V, to the earlier onset of the sexual season, and, in Groups I and V, to the greater activity during the earlier part of the sexual season (Tables II and III). If the number of dioestrous cycles occurring during the first period, when no treatments were given, are deducted then the total number of cycles of Groups IV and V are affected and they become 51 and 56 respectively.

The analysis upon the periodicity of oestrus given in Table III of the text, indicates the absence of abnormal interoestrous periods in Group I, while the other groups, which were shorn in February, have 7-8 per cent. abnormal interoestrous periods. The November-shorn groups, II, III, and VI, have 16, 3, and 15 per cent. abnormal interoestrous periods; Group III received no other treatment but the November shearing. The mode of the interoestrous period of all groups is seen to be 17 days.

From the above, it appears evident that early summer shearing tends to inhibit sexual activity during the first few months of the sexual season. It is suggested that constant rains on shorn sheep during the heavy rainfall months of December and January may bring about slight inhibition of sexual activity (Diagram I). No biological explanation can be offered for the irregularity.

Two groups of sheep, I and VI, were inoculated against bluetongue. In Group VI inoculation was done at the customary time. The reaction to the inoculation is expected to take place between the 7th to the 15th day.

In the case of Group VI, the inoculation was given before the onset of the sexual season and there is no direct evidence to indicate that the inoculation postponed the onset of the sexual season. In Group I, the injection was given on February 5th; and, subsequent to that date during the same month, 7 sheep exhibited oestrus, while the total number of dioestrous cycles was 10 (Appendix 7, Table VII). There is no evidence to indicate that the inoculation inhibited the occurrence of oestrus.

The dipping of sheep in short or long wool, or dipping early or late during the sexual season, has no influence upon the onset of the sexual season or the regularity of the dioestrous cycles. Detailed evidence of these effects may be obtained by consulting the records giving the dates of dipping or the occurrences of oestrus of Groups II, IV, and VI in Appendix 7, Tables VIII, X and XII. In 18 out of 20 cases of sheep which showed oestrus during the periods between dippings, oestrus recurred with normal regularity. Within 26 days after the second dipping, not a single abnormal interoestrous period occurred in 22 sheep which were active during that period.

The results of the examinations of the ovaries of the two sheep in Group III, in which oestrus had not been observed for 307 and 253 days, reveal that in one case ovulation had recently occurred (Table IV). The occurrences of spurious ovulations in such cases has been remarked upon in Experiment 2. In both cases relatively few Graafian follicles are present.

Conclusions.

1. Observations were made on the effects of inoculation, shearing, and dipping on the body weight and sexual activity of 60 Merino ewes.

2. Shorn and unshorn sheep experience similar rapid increases in weight during the spring and early summer months. Spring-shorn sheep regain their pre-shearing weights within 2 to 3 weeks after shearing, but sheep shorn during the latter part of summer do not reflect such gains after shearing.

3. An insignificant temporary drop in body weight occurs after inoculation.

4. An insignificant temporary drop in body weight occurs after dipping.

5. Marked individual differences of the time of the onset of the sexual season and the number of dioestrous cycles exhibited occur, irrespective of the type of management practice adopted.

6. Early summer shearing appears to result in slight inhibition of sexual activity during the earlier part of the sexual season. The onset of the sexual season of some individuals is postponed and the percentage of abnormally long interoestrous periods is increased. These conditions are suspected to be a result of constant rain upon the shorn animals. No biological explanation can be given.

7. In sheep which are inoculated annually, inoculation against bluetongue in no way inhibits sexual activity.

8. The dipping of sheep in short or long wool has no influence upon the regularity of sexual activity.

9. Spurious ovulations occur in cases in which oestrus is found to be absent during the entire sexual season.

EXPERIMENT 9.

Artificial Induction of Oestrus during Anoestrum.

The results reported in the preceding experiments indicate that Merino sheep, and certain types of crossbred sheep, experience restricted annual sexual activity under the conditions obtaining at the Research Station. The sexual season of the sheep under observation was limited to the autumn and winter months, while an anoestrous period was found to occur during the remaining seasons of the year. However, marked differences in the degrees of polyoestrum were observed in individuals and nutrition was found to play an important rôle in influencing the degree of polyoestrum exhibited by sheep.

Restricted sexual activity such as evidenced limits the lambing season to the winter, spring, and early summer months. Under farm conditions, the growth of lambs during these seasons is greatly inhibited; the reasons for the retarded growth of such lambs were mentioned in previous sections. (The Physiographical Conditions, etc., The Methods of Sheep Husbandry, and Experiment 6). Also, attention was drawn to the fact that many Merino sheep farmers in the eastern districts of the Transvaal regulate lambing to occur during two seasons, the autumn and the spring, and, for reasons previously stated, the former season is preferred. Ewes which do not mate, or which are not successfully mated, during the spring and early summer months, are mated in the autumn. Farmers in these districts maintain that the lambing season of Merino ewes may be altered from the spring to the autumn, provided the necessary precautions of management and mating are observed. In other words, it is contended that it is possible to affect an alteration in the rhythm of the sexual season of Merino sheep under the conditions obtaining in these districts. Further reference to this aspect will be made in the latter part of the discussion of this experiment.

Artificial methods of inducing normal oestrus and ovulation in animals in which, for various reasons, oestrus does not occur, have received considerable attention during the past decade (Robson, 1934). The artificial method involves the administration of gonadotropic hormones in the form of extracts prepared from one of the following: anterior pituitary lobe, pregnant mare's serum, placenta, pregnancy urine. The last appears to be the most suitable material for the production of large quantities of extract (Robson, 1934).

Warwick and co-workers (1933) used a serum prepared from human pregnancy urine on goats during anoestrum and, while ovulation was produced in several cases, oestrus was not exhibited. The only successful application of an artificial method of inducing normal oestrus and ovulation in sheep during anoestrum which has come to the author's notice is that of Cole and Miller (1933). These authors used gonad stimulating hormone, the source of which was untreated serum from pregnant mares. It is stated that a single injection of 50 R.U. or more, results in ovulation, but oestrus is not produced. Neither is oestrus induced by giving injections on several consecutive days. However, when a second injection of gonad stimulating hormone is given 16 days after the first injection, ovulation and oestrus result and a high percentage of fertility is obtained from matings made during such oestrous periods.

As Merino sheep under certain conditions exhibit a higher degree of polyoestrum than any other breed of the same species (Marshall, 1922; Quinlan and Maré, 1931), it may be thought that it would be more easy to induce ovulation and oestrus in Merinos during anoestrum in areas where restricted annual sexual activity is experienced.

" Prolan " is a standardized anterior pituitary hormone according to Zondek. The preparation is contended to bring about normal sexual activity resulting in successful fertilization in horses, cattle, and pigs, for which the required dosages are given as 125, 125, and 50 R.U. (rat units) respectively. No dosage is given for sheep.

The object of the experiment was to ascertain whether " Prolan " is capable of inducing normal oestrus during anoestrum in mature and young Merino sheep and in young crossbred sheep the dams of which were Merinos.

Materials and Methods.—The various sections, A to D, of the experiment were conducted during the anoestrous periods of the years 1933 to 1935. For the purpose of convenience, the portions are presented as one experiment which is seen to consist of nine groups of sheep (Table I).

The sheep used in the experiment were drafted from the Research Station's available flock, the general treatment of which has been described in a previous section (Experiment 1). However, in the case of Groups VIII and IX, the sheep had been under observation in Experiment 6 for 585 days before being utilized in this experiment.

Groups I to IV(*a*) consisted of mature Merino ewes, Groups V, VI, and VII each consisted of 5 Border Leicester-Merino and 5 Ryeland-Merino crossbreds 17 months old, and Groups VIII and IX consisted of Merino ewes 24 months old. It will be noticed that a control group was included in each of the five series of groups.

The sheep were tested for oestrus by means of vasectomised teasers once daily for at least 20 days prior to the first injection of " Prolan ", after which daily oestrous observations were continued. In the case of Groups VIII and IX, oestrous observations were made twice daily after the first injection of " Prolan ".

The precautions demanded in the instructions for the use of " Prolan " were observed. The inguinal regions of the sheep were washed without the use of soap and disinfectants, but the areas were sterilized with ether before the subcutaneous injections of " Prolan " were given.

The periods after which the various numbers of injections of " Prolan " were given to each group are indicated in the table of results.

With the exception of the sheep in Groups I and II, all sheep that showed oestrus during the period between injections and within 40 days subsequent to the last injection were control served by rams the fertility of which had been assured by sperm tests. Two services were given each sheep; the second service was allowed six hours after the first.

Results.

Table I gives complete details with respect to each of the Groups I to IX.

Discussion.

In the experiments reported here, 10 Merino ewes in Group II, treated with " Prolan " on 5.12.33, received 12·5 R.U. at each of two injections, the second injection having been given 7 days after the first.

It is seen that none of the sheep in the two groups exhibited oestrus during the period between injections, nor did sexual activity commence in Group II immediately after the second injection. In the control group, five sheep showed oestrus within 40 days after the second injection was given to Group II, and in the latter group 6 sheep showed oestrus during the same period. It has been seen in the results of previous experiments, that the sexual season of some Merino sheep may commence as early as the latter part of December (Experiments 1 and 8).

It may be concluded that " Prolan " had no effect in inducing oestrus in the treated sheep.

In section B, 20 Merino ewes were used in each of Groups III and IV, the latter group being given four injections of " Prolan " of 25 R.U. each at intervals of 6 days from 23.11.34.

It is seen that both in the control and the injected groups, one sheep showed oestrus during the periods between injections. Also, in each case three sheep exhibited oestrus and were served within 40 days subsequent to the last injection. In Group III (control), one showed a recurrence of oestrus after service, whereas in Group IV two returned for service. By 18.2.35, or 87 days after the first injection was given to Group IV, 9 sheep in Group III and 10 sheep in Group IV had not shown oestrus.

The above 19 sheep were used as a further test in which the 9 sheep of Group III constituted the control Group III (a) and the 10 sheep of Group IV constituted the treated Group IV(a).

Group IV(a) was given two injections of " Prolan " of 50 R.U. each at an interval of 16 days, or approximately the mode of dioestrum of Merino sheep (Experiment 3).

One control sheep exhibited oestrus between injections, and two of these sheep showed oestrus within 40 days subsequent to the last injection given Group IV(a). Four treated sheep showed oestrus within 40 days subsequent to the last injection. One of the former and two of the latter sheep returned for service. It should be noted that during the latter part of February a certain percentage of sheep may be expected to have entered the sexual season (Experiment 1).

The results of the two systems of treatment with " Prolan " are negative.

In section C, 30 crossbreds, Border Leicester-Merino and Ryeland-Merino, 17 months old were used for the observations. It is seen from Experiment 6 that sheep of this type are in anoestrum at this age, but that 100 per cent. sexual activity can be expected in such sheep during the following sexual season or when they are from 19 to 22 months old. Therefore the time of treatment was just prior to the sexual season of 1935.

Groups VI and VII were given two injections of " Prolan " each of 50 and 75 R.U. respectively at an interval of 17 days. It appeared from the results of Experiment 6 that the dioestrous cycle of crossbred sheep is slightly longer than that of Merino sheep.

One sheep in Group VI exhibited oestrus during the period between injections. One sheep in each of Groups V and VI, and two sheep in Group VII showed oestrus shortly after the date of the second injection of " Prolan ". The latter two sheep returned for service. The inactivity of the sheep in all three groups was marked during the period of observations or for 56 days.

The administration of " Prolan " failed to induce oestrus in these sheep.

The sheep in section D were comparatively well grown Merino ewes of 24 months of age. The sexual histories of these sheep have been given in the results of Experiment 6. Only 40 per cent. of these sheep had shown sexual activity during the previous sexual season (1934), when they were 19 to 22 months old. It may be expected that all these sheep will show sexual activity during the coming sexual season (1936) or when they attain the age of 28 or 29 months (Experiment 1A). The sheep of Group IX were subjected to treatment when, as evidenced in all previously reported experiments, sheep are most inactive under these conditions.

Group IX was given two injections of " Prolan " each of 100 R.U. at an interval of 14 days.

No sexual activity was observed in the control and in the treated groups, and the results from " Prolan " are, therefore, negative.

It must be mentioned here that no definite explanation can be given for the high percentage of infertility which resulted from the services given. It will be noticed that a total of 16 ewes in sections B and C was served and that only 50 per cent. fertility was established. As previously mentioned the rams used were sperm tested; the microscopic examinations of the semen revealed the presence of very large quantities of highly motile normal spermatozoa and, therefore, such rams may be considered to have been highly fertile (McKenzie and Phillips, 1933). As the numbers concerned are small, the probability of incomplete oestrus, or oestrus without ovulation,

TABLE I.

The Use of "Prolan" to induce Oestrus during Anoestrum.

Group.	No. of sheep.	Breed or type.	Age of sheep.	Mean weight of group at time of injection.	Period of testing for oestrus before first injection.	No. of sheep exhibiting oestrus within 40 day period preceding first injection.	Date of first injection.	No. of injections.	Periods between injections.	Quantity of "Prolan" given each sheep at each injection.	No. of cases in which oestrus occurred during the periods between injections.	No. of cases in which oestrus occurred within 40 days subsequent to the last injection, or after the following periods indicated in days (*a*). Days. 1.	2.	6.	7.	9.	10.	12.	13.	18.	20.	22.	23.	27.	28.	29.	30.	33.	35.	No. of cases in which oestrus did not occur throughout the entire period of testing (*b*).
				lb.	Days.				Days.	R.U.																				
A. I	10	Merino	Mature	76·0	20	—	Control	—	—	—	—	—	—	—	—	—	1	—	1	—	—	1	1	—	1	—	—	—	—	0 (167 days).
II	10	,,	,,	76·0	20	—	5.12.33	2	7	12·5	—	—	—	—	—		—	1	—	—	1	—	1	1	—	—	1	—	1	1 (,,).
B. III	20	Merino	Mature	71·3	20	—	Control	—	—	—	1	—	—	—	1	1	—	—	—	—	—	—	—	—	—	—	(1)	—	—	—
IV	20	,,	,,	70·4	20	—	23.11.34	4	6	25	1	—	—	(1)	—	—	—	—	—	(1)	—	1	—	—	—	—	—	—	—	—
III (*a*)	9	,,	,,	76·5	105	—	Control		—	—	1	—	—	—	—	—	—		1	—	—	—	—	—	(1)	—	—	—	—	7 (63 days).
IV (*a*)	10	,,	,,	74·3	105	—	18.2.35	2	16	50	—	—	—	—	—	—	—	(1)		—	—	—	—	—	1	(1)	—	1	—	6 (,,).
C. V	10	Crossbreds	17 mths.	67·0	20	2	Control	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	9 (56 days).
VI	10	,,	,,	65·2	20	—	28.2.35	2	17	50	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	9 (,,).
VII	10	,,	,,	69·5	20	—	28.2.35	2	17	75	—	—	(2)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	8 (,,).
D. VIII	5	Merino	24 mths.	62·2	585	—	Control	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5 (136 days).
IX	5	,,	,,	62·2	585	—	1.10.35	2	14	100	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5 (,,).

NOTE.—(*a*) With the exception of the sheep in Groups I and II, all sheep showing oestrus within the 40 day period were served. The cases which were not fertilized by such services have been placed in brackets.

(*b*) The length of the entire period of testing for oestrus is indicated in brackets in this column. In the case of Groups VIII and IX, the period has been considered from the date of the last occurrence of oestrus during the previous sexual season.

cannot be considered. No experimental evidence is available to indicate that low fertility results when ewes are mated at the onset of their sexual seasons.

The possibility of artificially inducing normal oestrus by the administration of gonad stimulating hormones is a matter of considerable practical importance to stud and flock owners.

Stud breeders frequently find that valuable animals will not breed. It is not known whether the majority of such cases of infertility are due to the presence of pathological conditions resembling some of those encountered in bovines (Hammond, 1927; Quinlan, 1929), or to obesity as suggested by Quinlan and Maré (1931), or merely to an unaccountable quiescent or even static state of the ovaries perhaps due to the absence of breeding. The probability exists that, in certain cases, the mating of such sheep is restricted to a particular time, and that such individuals may experience exceptionally few dioestrous cycles during the entire year, as has been evidenced to occur in certain sheep under observation in many of the experiments reported in this thesis. However, it is possible that the administration of gonadotropic hormones may overcome some of the causes of infertility in stud sheep, and that, once the genital organs are set in motion, normal annual reproduction will result.

Whether the application of successful artificial methods of inducing normal oestrus will be extended to flocks will depend upon the price of the preparations. In general flock practice, unproductive ewes are marked and eventually culled during the annual classing. However, a problem of great concern to the flock owner is that of obtaining a high percentage of lambs at a time which is most favourable for the health and growth of the lambs.

Previous mention has been made of the fact that both autumn and spring-born lambs are obtained in these districts. The author has been in intimate contact for three years with the mating operations during the spring months of two Merino sheep farmers within a radius of 14 miles of the Research Station. These owners employed the system of control serving, and, during the months of October and November, large numbers of ewes were served, while during those months at the Research Station, the sheep under observation were in anoestrum. The assurance given by experienced sheep farmers, that the season of lambing of Merino ewes under these conditions, may be altered from the spring to the autumn months by careful regulation of the time of mating, by early weaning of the lambs, and by maintaining the sheep in good condition, suggests an an explanation for the existence of two lambing seasons. No doubt is expressed as to the possibility of the alteration of the period of lambing, although the method of effecting the change has not been subjected to experimentation. It is not known whether it is possible to convert all Merino sheep, whether the sexual season of the converted sheep occupies the full period of anoestrum of spring lambing sheep, whether in the absence of breeding the former sheep revert back to the condition in which the sexual season is restricted to the autumn and winter months, and whether autumn lambing sheep experience a shorter anoestrum or one of equal length to that of spring lambing sheep.

During several years of experience in the eastern Transvaal highveld, the author has constantly come in contact with sheep farmers who have become alarmed about the abnormally low lambing percentages obtained by them, cases in which lambing results as low as 50 and 40 per cent. have been reported.

Many farmers have observed a tendency of their ewes to lamb in the spring rather than in the autumn. In a recent number of an agricultural periodical (*Farmer's Weekly*, November 13, 1935), a Karroo farmer remarks upon "ewe idiosyncrasies". He states that it is exceedingly difficult to obtain more than half his lambs from the October to December mating, that some ewes have never lambed in the autumn, although they have lambed with great regularity in the spring, and he concludes that some ewes are willing to lamb only in the spring.

The above general remarks have been made in order to present briefly the problems encountered by Merino stud and flock owners, and to indicate the field for the application of scientific measures for ensuring higher fertility, which would assist very materially in rendering the sheep enterprise more remunerative.

Conclusions.

1. A standardized anterior pituitary hormone, "Prolan", was given subcutaneously with the object of inducing normal oestrus in Merino and crossbred sheep during anoestrum.

2. The following methods of administering the hormone failed to induce oestrus in the types of sheep mentioned:—

(*a*) Mature Merino ewes received two injections of 12·5 R.U. each at an interval of 7 days.

(*b*) Mature Merino ewes received four injections of 25 R.U. each at intervals of 6 days.

(*c*) Mature Merino ewes received two injections of 50 R.U. each at an interval of 16 days.

(*d*) Merino ewes 24 months of age received two injections of 100 R.U. each at intervals of 14 days.

(*e*) Border Leicester-Merino and Ryeland-Merino crossbreds 17 months of age received two injections of 50 R.U. each at an interval of 17 days.

(*f*) Border Leicester-Merino and Ryeland-Merino crossbreds 17 months of age received two injections of 75 R.U. each at an interval of 17 days.

3. The field for the application of artificial methods of inducing oestrus in commercial studs and flocks is discussed.

PART 2.

THE REFLECTION OF SOME PRINCIPLES OF SEX PHYSIOLOGIY IN PRACTICAL SHEEP HUSBANDRY.

The data presented and discussed in this section have not been obtained from experimental findings, but by analysing:—

A. Extracts from Merino stud registers.

B. The observations of reliable stud breeders in various parts of South Africa upon the breeding habits of sheep .

The results of the analysis of such records and observations have not been appended to attempt to render the experimental findings reported in this thesis more complete, but rather with the view of presenting some information, although limited, to indicate the ways in which some principles of sex physiology are expressed under practical conditions of sheep husbandry. It is contended that closer observation and the analysis of breeding records will assist very materially in elucidating many practical breeding problems, which are of immense and far-reaching economic importance.

A. The Analysis of Extracts from Merino Stud Registers.

It is not desired that animals should be compelled to reproduce when the process would endanger normal growth and development, yet it is most certainly of great economic importance that best use should be obtained of the full length of the period of the animal's life during which reproduction is possible.

The main object of this analysis is to obtain information upon the length of the reproductive life of Merino ewes belonging to studs at Government Institutions, in which modern methods of management, selection, and breeding have been practised for very many years. It is possible that the results will suggest methods of management, selection, and breeding which would tend to improve fertility in studs.

(*a*) *Mating Maiden Merino Stud Ewes.*

The results of mating Merino ewes in three Studs A, B, and C, maintained under Cape (Karroo), Transvaal, and Free State conditions respectively, have been analysed, and the respective results are given in Tables I, II, and III.

It will be noticed that in the Case of Stud A, Table I, the control or hand service method of mating was employed, while, in studs B and C, the small paddock system of mating was used; consequently, the information with regard to Stud A is more complete than in the cases of the latter two studs.

TABLE I.

MATING MAIDEN MERINO STUD EWES.

Stud A: (Controlled or Hand Service Mating).

Mating season.	Total No. of ewes available for mating.	Age at time of mating.		Ewes mated.		Lambs out of ewes mated.		Lambs from Total No. of available ewes.
		Range.	Average.	No.	Per cent. of total.	No.	Per cent.	
		Months.	Months.					Per cent.
1929.......	33	16–19	17·3	23	69·7	15	65·2	45·5
1930 (*a*)*...	9	19–21	19·8	9	100·0	5	55·6	55·6
1930 (*b*)....	32	22–27	25·9	26	81·2	13	50·0	40·6
1931.......	52	15–23	19·9	52	100·0	37	71·2	71·2
1932.......	41	18–26	20·1	32	78·0	19	59·4	46·3
1933 (*c*)....	63	15–21	18·8	46	73·0	29	63·0	46·0
1933 (*d*)....	22	24–27	25·2	16	72·7	10	62·5	45·4
For all seasons...	252	15–27	21·0	204	81·0	128	62·7	50·8

*NOTE.—(*a*) Sheep were born in the autumn and mated in the spring at 19·8 months.
(*b*) Sheep were born in the autumn and mated in the autumn at 25·9 months.
(*c*) Sheep were born in the autumn and mated in the spring at 18·8 months.
(*d*) Sheep were born in the spring and mated in the spring at 25·2 months.

TABLE II.

Stud B: (Small Paddock Mating).

Mating season.	Total No. of ewes mated.	Average age at time of mating.	Lambs born.	
			No.	Per cent.
		Months.		
1929..................	11	—	5	45·4
1930..................	2	21	1	50·0
1931..................	8	18	4	50·0
1932..................	7	21	3	42·8
1933..................	17	25	6	35·2
1934..................	16	21	11	68·8
For all seasons.....	61	21·2	30	49·2

TABLE III.

Stud C: (Small Paddock Mating).

Mating season.	Total No. of ewes mated.	Average age at time of mating.	Lambs born.	
			No.	Per cent.
		Months.		
1930.................	31	21	20	64·5
1931.................	34	19	11	32·4
1932.................	16	20	3	18·8
1933.................	21	20	8	38·1
For all seasons.....	102	20	42	41·2

Discussion.

Quinlan, Maré, and Roux (1930) state that Merino ewes show oestrus regularly at the ages of 9 to 10 months,; 100 per cent. sexual activity was observed at that age.

The usual stud practice is to mate maiden ewes when they are 18 to 20 months old; at this age such sheep are well grown and pregnancy does not inhibit further development, so that by the end of the gestation period, the sheep are approximately 24 months old, fully grown, and able to stand the more severe strain of lactation (Parkes 1929).

It is seen from Tables I, II, and III that the ages of mating conform to the above stud practice, except in the case of the 1930 (*b*) season when autumn-born lambs were mated in the autumn at 25·9 months of age, and the 1933 (*d*) season when spring-born lambs were mated in the spring at the age of 25·2 months (Stud A, Table I).

The percentage of the available ewes actually served was obtainable only in the case of Stud A, in which controlled serving was practised; this percentage during the seven mating seasons is seen to range between 69·7 and 100 per cent., the average being 81·0 per cent. (Table I). The fertility established in these matings is given, and it is seen to range between 50·0 and 71·2 per cent., the average for the seven seasons being 62·7 per cent. Yet more interesting, are the percentages of lambs obtained from the total number of available maiden ewes; this figure ranges between 40·6 and 71·2 per cent., the average being 50·8 per cent. (Table I).

These percentages of successful matings in the case of Stud A, may be compared with those in Studs B and C, in which small paddock mating was practised. Marked variations in fertility occur also in the latter two studs, and the fertility for all seasons is equally poor in the case of Stud B, being 49·2 per cent. (Table II), and appreciably poorer in the case of Stud C, being 41·2 per cent. (Table III). The results in the latter case are for only four seasons, but 102 sheep are involved.

It is very evident that the fertility of Merino stud ewes 18 to 25 months old in the studs examined is very low. The infertility of such ewes is due to approximately 20 per cent. of the ewes not showing oestrus during the mating period, and approximately 40 per cent. of the ewes mated not being fertilized.

In connection with the results obtained in the case of Stud A, it is of interest to consider the types of seasons experienced. For the particular area, the South African Karroo, the rainfall records are considered an excellent guide; these records are given in Table IV.

By studying the results reflected in Table I and the rainfall records in Table IV, it is not evident that a high correlation exists between high sexual activity (ewes mated) and high rainfall, or high fertility (successful matings) and high rainfall. Both 1928 and 1929 were average to good rainfall years, and abundant spring rains were experienced during 1929; yet only 69·7 per cent. of ewes were served, 65·2 per cent. of which lambed, and only 45·4 per cent. of the total number of ewes lambed. The rainfall during 1930 was only 8 inches, the spring rains in 1931 were late, and not much rain was experienced even during October and November, the months of mating; yet 100 per cent. of ewes were mated, and the percentage fertility reflected in the number of lambs obtained, 71·2 per cent., was higher than that of any other season.

Interesting information with regard to the influence of season of birth upon the eventual seasonal sexual activity has become available in the analysis of the records of Stud A.

Russell (1919), working with Rambouillets and several British breeds and their crosses in the United States, considers that evidence was revealed which indicates that spring-born lambs tend to produce spring lambs, and autumn-born lambs tend to produce autumn lambs.

In this connection, the following extracts taken from Table I are of interest:—

(1) In the season 1930 (*a*), 100 per cent. of sheep born in the autumn were mated in the spring at 19·8 months of age, and 55·6 per cent. fertility was obtained.

(2) In the season 1930 (*b*), 81·2 per cent. of sheep born in the autumn were mated in the autumn at 25·9 months of age, and 50 per cent. fertility was obtained.

(3) In the season 1933 (*c*), 73·0 per cent. of sheep born in autumn were mated in the spring at 18·8 months of age, and 63 per cent. fertility was obtained.

(4) In the season 1933 (*d*), 72·7 per cent. of sheep born in the spring were mated in the spring at 25·2 months of age, and 62·5 per cent. fertility was obtained.

It is evident that the above information upon young Merinos under South African Karroo conditions, does not bear out Russell's contention.

TABLE IV.

Rainfall Records: Area of Stud A.

Year.	Jan.	Feb.	March.	April.	May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Total.
1928................	2·61	0·76	2·04	1·25	0·04	0·05	0·03	0·13	1·38	0·80	1·11	1·51	11·73
1929................	1·78	0·89	2·28	0·12	1·44	0·41	1·42	0·74	4·01	1·78	1·61	1·97	18·45
1930................	2·08	0·63	3·36	0·24	0·27	0·49	0·02	0·28	0·04	0·47	0·58	0·40	8·86
1931................	2·66	0·94	2·61	0·97	0·00	0·10	2·94	0·07	0·06	1·15	1·75	2·91	16·16
1932................	0·35	1·59	1·32	0·06	0·58	0·00	0·42	0·00	2·39	0·47	1·79	1·33	10·30
1933................	0·90	0·38	3·24	1·02	0·02	0·05	0·26	0·56	0·41	0·00	4·92	2·53	14·29

Conclusions.

1. Data were obtained by considering a total of 415 maiden Merino ewes in three studs maintained under Cape (Karroo), Transvaal, and Free State conditions.

2. Approximately 20 per cent. of maiden Merino ewes, between the ages of 18 to 25 months, do not experience a continuous series of dioestrous cycles during the recognized mating seasons. Under South African Karroo conditions, mating may be undertaken in the autumn and spring seasons.

3. Approximately 40 per cent. of maiden Merino ewes mated are not rendered fertile.

4. The percentage of maiden Merino ewes that lamb during the ages of 23 to 30 months is only 41 to 51 per cent.

5. The controlled service method of mating has the advantage of revealing cases in which sexual activity is absent and in which fertility has not been established by mating. This method of mating is recommended in the case of maiden ewes, because it indicates the need for extending the mating period. It is considered desirable to set the reproductive processes of young ewes in motion as soon as possible after they are 18 months of age.

(*b*) *The Breeding Histories of Prolific Merino Ewes.*

The breeding records of thirty of the most prolific ewes have been extracted from each of three Merino stud registers. The studs are referred to as Studs A, B, and C, which were maintained under Cape (Karroo), Transvaal, and Free State conditions respectively. The details of individual ewes in the studs are given in Tables V, VI, and VII respectively.

Table VIII has been constructed from the above Tables V to VII in order to permit a comparison of the different studs.

Discussion.

No data upon the reproductive capabilities of stud Merino sheep under South African conditions have been analysed and published. There is no doubt that a more intimate knowledge of the breeding histories of the individuals in studs would assist greatly in the establishment of higher fertility, as this character, like all body characters, has a genetic basis.

While it is realised that a more thorough analysis embracing animals of high and low fertility would yield more valuable information, so complete an analysis is not possible here owing to the excessive amount of data that would have to be presented. By considering the 30 most prolific ewes on record in each of three studs, a conception of the highest degree of fertility in these studs will be obtained and this will serve as a guide.

Age at First Successful Mating.—In Stud A, the ewes were born during the years 1921 to 1926 (Table V). The ages at the first successful matings ranged between 18 and 32 months, the average being 21·0 months (Table VIII). It has been computed from the former table that 90 per cent. of the ewes were successfully bred at the ages of 18 to 24 months.

TABLE V.

The Breeding Histories of the Most Prolific Ewes in Merino Stud Register A.

Sheep No.	Date of birth.	Age at first successful mating.	Life period of lambing.	No. of lambs produced	Sets of twins.	Present age or age at disposal or death.	Spring lambing preceded by, and followed by autumn lambing.	Non-lambing years.	Remarks.
		months.	years.			years.	dates.		
D.B. 114.	20.4.24	19·25	7·0	10	2	8·75	—	—	Died 1933.
M 603....	23.6.23	18·25	9·25	13	4	11·5	13.3.32, 20.10.33	—	In stud.
M 611....	29.6.23	20·25	6·5	9	2	—	—	1926	Disposed of—old.
M 761....	5.6.25	18·5	5·75	6	—	8·0	—	—	Missing 1933.
M 880....	7.4.26	19·5	5·75	6	—	8·0	25.3.30, 4.10.31, 8.3.33	1932	Sold 1934.
T 343....	5.6.25	19·5	6·5	8	1	8·0	—	—	Died 1933.
T 384....	19.4.26	22·0	8·25	11	3	8·75	7.5.30, 7.10.31, 17.4.32, 28.3.33, 20.10.33	—	In stud.
T 307....	3.6.24	22·0	5·75	6	—	7·0	—	—	Died 1931.
T 331....	3.6.24	18·75	5·75	6	—	10·0	—	—	Discarded 1934.
T 367....	2.4.26	22·0	6·5	7	—	8·0	22.4.30, 4.10.31, 27.6.32	—	Sold 1934.
D.B. 123.	20.5.22	31·75	7·75	10	4	12·0	—	1928, 1929	Culled 1934.
T 287....	16.6.23	28·5	8·75	11	2	11·0	—	—	Died 1934.
T 293....	25.6.23	18·0	8·75	9	—	11·0	—	—	Missing 1934.
T 338....	5.6.25	18·25	7·75	10	2	9·75	—	—	In stud.
D.B. 95..	21.3.26	20·5	7·75	10	3	8·0	26.9.31, 26.4.32	1930	Discarded—old age, 1934.
D.B. 91..	5.6.21	29·5	8·75	8	—	11·0	1.5.26, 25.3.27, 24.6.28	—	Discarded 1932.
D.B. 109.	13.4.26	22·0	5·25	6	—	7·0	—	—	Died November, 1933.
M 807....	22.6.25	24·75	7·25	8	—	9·0	—	—	Discarded 1934.
M 440....	30.4.21	24·0	6·5	8	1	10·0	15.3.23, 22.6.24	—	Died 1931.
D.B. 113.	20.4.24	19·5	7·75	10	2	9·0	—	—	Died December, 1933.
M 882....	9.4.26	19·5	6·75	9	2	8·0	9.4.30, 24.9.31, 8.7.32	—	Discarded 1934, still alive.
M 731....	26.5.25	22·0	6·5	9	2	10·0	8.9.27, 30.5.28	—	In stud.
M 756....	26.5.25	19·0	5·75	8	2	8·0	—	—	Missing 1933.
M 789....	11.6.25	18·75	7·75	9	1	9·0	—	—	Discarded 1934.
M 599....	1.7.23	20·0	8·5	9	—	11·0	—	—	Culled 1934.
M 534....	2.5.22	21·0	10·5	11	1	12·0	—	1925	In stud.
M 830....	21.4.26	21·25	7·25	10	3	8·0	30.3.33, 20.10.33	—	Died 1934.
T 268.....	17.4.22	20·0	8·75	10	1	10·0	—	—	Died 1932.
T 278....	6.5.23	19·5	8·75	10	1	11·0	—	1927	Died 1934.
T 282....	27.5.23	19·5	8·75	11	2	11·0	—	—	Died 1934.
Totals....	—	638·0	222·5	269	41	273·75		7	—
Averages..	—	21·0	7·42	9	—	9·12	—	—	—

TABLE VI.

The Breeding Histories of the Most Prolific Ewes in Merino Stud Register B.

Sheep No.	Date of birth.	Age at first successful mating.	Life period of lambing.	No. of lambs produced.	Sets of twins.	Present Age or age at disposal or death.	Non-lambing years.
		months.	years.			years.	
1295 Z	2.5.18	33	8	7	—	11·75	1926
3 C 48	19.4.23	32	6	7	2	10·25	1928
3 D 63	5.4.23	33	4	5	1	7·0	—
4 C 80	21.3.24	44	4	7	3	9·25	—
4 C 87	18.4.24	55	4	5	1	9·5	—
3 B 31	29.3.33	31	7	7	—	12·0	—
3 B 49	29.3.23	55	4	5	1	12·0	—
3 HR 57	4.4.23	55	4	4	—	10·0	—
3 D 71	20.4.23	45	6	5	—	10·5	—
S D J 127	15.5.25	42	5	6	1	10·0	—
6 G 201	24.4.26	31	5	5	—	9·0	—
6 H 251	7.4.26	43	6	5	1	9·0	1932
6 C 253	21.4.26	20	7	6	1	9·0	1933, 1934
1470	15.3.22	60	5	6	1	11·25	—
1459	15.3.22	32	5	5	—	11·0	—
1478	15.3.22	32	7	5	—	11·25	1928, 1929
1483	15.4.22	45	5	4	—	11·0	1928
1486	15.4.22	55	5	6	1	10·25	—
1487	17.4.22	45	5	6	1	11·5	—
1490	18.4.22	31	7	6	—	11·25	1928
1602	15.4.24	23	7	8	2	9·25	1928
1603	15.4.24	23	4	4	—	8·75	—
1616	15.4.24	18	5	4	—	9·0	1930
1435	15.4.21	43	5	4	—	12·5	1928
1426	10.6.21	41	4	4	—	12·0	1932, 1933
1391	15.4.21	69	4	4	1	12·25	1931
5 Q 123	15.4.25	23	6	4	—	10·75	1931, 1933
6 C 234	26.4.26	21	7	4	—	9·0	1932, 1933, 1934
6 H 235	26.3.26	22	6	4	—	9·25	1932, 1934
1604	15.4.24	23	4	4	—	8·75	—
Totals	—	1,125	161	156	17	308·25	22
Average	—	37·5	5·25	5·2	—	10·5	—

TABLE VII.

The Breeding Histories of the Most Prolific Ewes in Merino Stud Register C.

Sheep No.	First lambing recorded.		Life period of lambing.	No. of lambs produced.	Sets of twins.	Present age or age at disposal or death.	Non-lambing years.	Remarks.
	Age.	Year.						
	months.		years.			years.		
D.O.A. 11	18–24	1914	8	9	1	11	—	Died 1923.
D.O.A. 54	,,	1915	9	10	1	11	1916	Died 1924.
90	,,	1914	8	9	3	13	1915, 1916, 1920	Died 1925.
102	,,	1917	8	7	—	11	1918	Died 1926.
106	,,	1916	9	9	—	10	—	Died 1924.
107	,,	1916	9	9	—	11	—	Died 1925.
118	,,	1916	8	8	—	9	—	Died 1923.
381	,,	1920	8	8	—	9	—	Died 1927.
531	,,	1921	10	8	—	11	1927, 1928, 1923	Missing.
586	,,	1921	7	7	—	9		Culled—old age.
594	,,	1921	7	7	—	11	—	Culled 1930.
595	,,	1921	9	9	—	12	—	Slaughtered 1931—old.
601	,,	1921	8	8	—	12	—	Killed 1931—old.
602	,,	1922	9	12	3	11	—	Slaughtered 1931—old.
617	,,	1921	8	11	3	12	—	Slaughtered 1931—old.
625	,,	1921	7	9	2	10	—	Died 1929.
632	,,	1921	10	12	2	13	—	Culled 1932.
640	,,	1921	9	9	—	12	—	Killed 1931—old.
644	,,	1921	10	11	1	11	—	Culled 1930—old.
652	,,	1921	9	14	5	11	1923	Died 1930.
686 E	,,	1922	8	10	2	10	1923	Culled 1930.
684 E	,,	1922	9	11	2	11	—	Missing.
724	,,	1923	8	8	—	11	—	Missing.
725	,,	1924	9	11	2	10	—	Culled 1932.
727	,,	1924	9	11	2	11	—	Culled 1932.
731	,,	1923	9	10	1	11	—	Slaughtered 1932—old.
732	,,	1923	9	11	2	11	—	Culled 1932.
777	,,	1925	6	8	3	11	1927	Culled 1931.
923	,,	1927	7	8	1	10	1933	In stud.
62	,,	1929	6	10	4	8	—	In stud.
Totals	—	—	250	284	40	324	12	
Averages	—	—	8·25	9·25	—	10·75	—	

TABLE VIII.

The Breeding Histories of the Most Prolific Ewes in Three Merino Studs.

Stud (*c*).	Age at first successful mating.		Life period of lambing (years).								No. of lambs produced.													Sets of twins.						Total non-lambing years (*c*).	Final average ages (*b*) (years).		
	Range.	Average.	Average.	Frequencies (*a*).							Total.	Average.	Frequencies.											Total No.	Frequencies.						Present in stud.	Disposed of.	At death.
				4	5	6	7	8	9	10			4	5	6	7	8	9	10	11	12	13	14		1	2	3	4	5				
	months	months																															
A. (30)...	18–32	21·0	7·42	—	1	10	4	7	7	1	269	9·0	—	—	5	1	4	7	8	4	—	1	—	41	6	9	3	2	—	7 (6)	10·4	9·3	9·0
B (30).....	18–69	37·5	5·25	9	9	5	6	1	—	—	156	5·2	11	8	6	4	1	—	—	—	—	—	—	17	10	2	1	—	—	22 (15)	—	—	—
C (30)....	18–24	—	8·25	—	—	2	4	9	12	3	284	9·4	—	—	—	3	7	7	4	6	2	—	1	40	5	7	4	1	1	12 (9)	9·0	10·8	11·0

NOTE :—

(*a*) For the life period of lambing frequencies, the ages of the sheep were considered to the nearest 12 months.

(*b*) In the case of the final average ages given, sheep culled are included under the heading "disposed of" and sheep slaughtered are included under the heading "at death" as the latter may be considered to have reached an unproductive stage.

(*c*) The numbers in brackets indicate the number of individual sheep involved.

In Stud B, with the exception of one ewe, No. 12952, the ewes were born during the same years as those of Stud A (Table VI). In Stud B, the ages of the first successful matings ranged between 18 and 69 months, the average being 37·5 months (Table VIII). It has been computed from the former table that only 26·7 per cent. of the first successful matings occurred during the ages of 18 to 24 months.

In the case of Stud C, the ewes were born during the years 1914 to 1917 and 1920 to 1929. The exact date of birth of the ewes is not available, but it has been reported that the sheep were successfully mated at the ages of 18 to 24 months (Table VII).

Life Period of Lambing.—The life period of lambing is a figure of particular interest, as it not only indicates the duration of the reproductive period, but also reflects the general ability of the sheep to exist under the particular conditions. The value of the figure is reduced somewhat by the presence of sheep which were reported as "missing"; also, some individuals are at present in the studs so that their reproductive periods may not have terminated.

The life periods of lambing of the three studs are reflected in the ultimate analysis presented in Table VIII, in which the periods have been considered to the nearest 12 months. The periods are seen to range from 5 to 10 years, 4 to 8 years, and 6 to 10 years in Studs A, B, and C respectively, and the respective averages are 7·42, 5·25, and 8·25 years. The frequency columns indicate that, in the case of Stud A, the modal life period of lambing is only 6 years, although in 50 per cent. of cases this period extends between 8 and 10 years. In Stud B, the modes are only 4 and 5 years, and nearly 50 per cent. have a life period of lambing between 4 and 6 years. The period, in the case of Stud C, is appreciably longer; the mode is 9 years, and in 80 per cent. of cases the life period of lambing is 8 to 10 years.

Number of Lambs Produced.—The Merino is not a fecund breed; twins and triplets are not frequently produced. As the Merino is essentially a wool producing breed, it is not unlikely that selection for wool qualities has been carried out to the detriment of fertility. In this connection, it is of interest to mention a case of abnormal fecundity reported by Pearl (1913), of a ewe which gave 19 fleeces and bore 36 full grown lambs among which there were 7 sets of twins and 6 sets of triplets. It is also of interest to place on record a case reported by Mr. Gadd, Springfield, Tafelberg, Cape, of a Blackhead Persian ewe that attained the age of 28 years during which time she bore and reared 30 lambs.

An analysis of the lambs produced by the three studs under consideration is given in Table VIII.

The average number of lambs produced by Studs A, B ,and C was 9·0, 5·2, and 9·4 respectively.

The frequency columns of the table reveal further details. In Stud A, the mode of the number of lambs produced is 10, in Stud B only 4, and in Stud C 8 and 9. In 66·7 per cent. of cases in Studs A and C, 9 to 13, and 9 to 14 lambs were produced respectively, whereas in Stud B ,the maximum number of lambs produced was only 8, and in 63·3 per cent. of cases only 4 and 5 lambs were produced.

In the case of Stud A, certain ewes produced lambs during the autumn and during the following spring (Table V). This would increase the number of lambs that would have been produced beyond the number likely to have resulted, if the usual one annual lambing had been practised.

Sets of Twins.—The fecundity of the ewes is reflected in the sets of twins produced (Table VIII).

The total number of sets of twins produced is nearly similar in Studs A and C, namely 41 and 40 respectively; the equivalent figure for Stud B is only 17. Twins were produced by 66·7 per cent. of cases in Stud A, 43·3 per cent. in Stud B, and 60·0 per cent. in Stud C (Tables V, VI, VII). In Studs A and C the modal number of sets of twins produced during a life period is two, and in Stud B one.

Non-lambing Years.—The non-lambing years indicate the absence of reproduction and they are to be considered in estimating the fertility of a stud.

The total number of non-lambing years in Studs A, B, and C were 7, 22, and 12 respectively, and these occurred in a total life period of lambing years of 222·5, 161, and 250 respectively (Tables V, VI, and VII).

In Stud A, five sheep missed one, and one sheep missed two lambing seasons (Table V). In Stud B, nine sheep missed one, five sheep missed two, and one missed three lambing seasons (Table VI). In Stud C, seven sheep missed one, one sheep missed two, and one sheep missed three lambing seasons (Table VII).

Autumn and Spring Lambing.—In general practice, it is not desired that ewes that lamb in the autumn should lamb during the next spring, because of the heavy drain on the sheep. In some areas the possibility of such intensive reproduction in the case of Merinos would be questioned.

Parkes (1929) states that there is no cyclical ovarian change during lactation in the sheep, but Quinlan and Maré (1931) found that, in Merinos under South African Karroo conditions, ovulation may occur within 10 to 15 days following normal parturition and the latter authors state that such " ovulation is not accompanied, as a rule, by the physiological exhibition of heat when the ewe suckles her lamb ", although when the lamb is still-born " ovulation accompanied by normal oestrus may occur as early as 17 days after parturition ".

The analysis given in connection with Stud A, Table V, contains some data upon this phase. Such data have been extracted and presented in the following Table IX, which contains the lambing dates of cases in which spring lambing was preceded and followed by autumn lambing. The period between lambings, or the intermediate period, has been divided into the gestation period and the period of lactation and rest. Quinlan, Maré, and Roux (1932) found the gestation period of Merino sheep to be 151 days; this figure has been used to determine the period of lactation and rest. Unfortunately the exact ages at which the lambs were weaned are not known, but the practice at the institution is to wean lambs at the age of 3½-4 months.

TABLE IX.

Autumn and Spring Lambing.

Sheep No.	Autumn lambing.	Spring lambing.	Intermediate period.			Autumn lambing.	Intermediate period.		
			Total.	Gestation.	Lactation and rest.		Total.	Gestation.	Lactation and rest.
	Date.	Date.	Days.	Days.	Days.	Date.	Days.	Days.	Days.
M. 603	13.3.32	20.10.33	584	151	433	—	—	—	—
M. 880	25.3.30	4.10.31	556	151	405	8.3.33	881	151	730
T. 384	7.5.30	7.10.31	516	151	365	17.4.32	189	151	38
T. 384	28.3.33	20.10.33	204	151	53	—	—	—	—
T. 367	22.4.30	4.10.31	163	151	12	27.6.32	263	151	112
D.B. 95	—	26. 9.31	—	—	—	26.4.32	211	151	60
D.B. 91	1.5.26	25. 9.27	510	151	359	24.6.28	270	151	119
M. 440	—	15. 9.23	—	—	—	22.6.24	278	151	127
M. 882	9.4.30	24. 9.31	531	151	380	8.7.32	285	151	134
M. 731	—	8. 9.27	—	—	—	30.5.28	262	151	111
M. 890	30.3.33	20.10.33	202	151	51	—	—	—	—

From Table IX it appears that in some cases successful mating took place a relatively short period after parturition, indicating that ovulation and oestrus occurred at that time.

The periods from parturition to the time of the next successful mating which resulted in the alteration of the season of lambing were: 12, 38, 51, 53, 60, 111, 112, 119, 127, 134, 359, 365, 380, 405, 433, and 730 days. In general practice, the lactation period and the period of rest before mating takes place, make up a total of 214 days. Hence, the above periods of 12 to 134 days are exceptionally short, and the periods of 359 to 730 days are abnormally long. It must be pointed out that, in the above instances of short rest periods, only in the case of the 38-day period did the lamb die at or shortly after birth. In the other cases in which the lactation and rest periods were 12 to 134 days, the lambs are reported to have suckled their dams; these are, therefore, cases of exceptional early ovarian activity after parturition. The longer periods of 359 to 730 days indicate that, for some reason or other, mating, or perhaps successful mating, did not occur at the usual time. However, it must be noted that successful mating did eventually occur during a season other than that during which the previous successful mating took place.

Conclusions.

1. The breeding histories of a total of 90 of the most prolific Merino ewes out of three studs maintained under Cape (Karroo), Transvaal, and Free State conditions, have been analysed.

2. The age at the first successful mating:—

   (*a*) Under Karroo conditions, 90 per cent. of prolific ewes are successfully mated at the ages of 18 to 24 months. The average age for all cases is 21 months.

   (*b*) Under Transvaal conditions, approximately 27 per cent. of prolific ewes are successfully mated at the ages of 18 to 24 months. The average age for all cases is 37·5 months.

   (*c*) The same information is not available for Free State conditions, but it appears that the most prolific ewes can be successfully bred between the ages of 18 to 24 months.

3. The life period of lambing is influenced greatly by the age at which the first successful mating occurs. When the first reproduction occurs at the normal age (23 to 29 months), the average life period of lambing of prolific ewes is approximately 8 years, but when the first lambing is postponed, the average is reduced by approximately 3 years.

When the first reproduction occurs at the normal age (23 to 29 months), the life period of lambing of 50 to 80 per cent. of prolific ewes is 8 to 10 years.

When the first reproduction is postponed, the life period of lambing is approximately 5 years, and approximately 50 per cent. of cases have a life period of lambing between 4 and 6 years.

4. The number of lambs produced is influenced greatly, but not entirely, by the life period of lambing. During a normal life period of lambing of prolific ewes, approximately 67 per cent. of ewes produce 9 to 14 lambs, the average being approximately 9 lambs.

In cases in which the first lambing is postponed, 63 per cent. of the ewes produce only 4 and 5 lambs, and the average production of all ewes is 5·2 lambs.

5. The fecundity of the ewes is reflected in the number of sets of twins produced.

In the cases in which reproduction commences at the normal age, twins are produced by 60 and 67 per cent. of the ewes, and the total number of sets of twins produced in approximately 40.

In the case in which the first lambing is postponed, 43 per cent. of the ewes produce twins, and the total number of sets of twins produced is 17.

6. The presence of non-lambing years reflects inconsistency in breeding, but when a large number of individuals is considered, a certain number of unproductive years appears to be permissible.

Considering the total life periods of lambing years of the two more highly productive studs, A and C, the non-lambing years amount to 3·1 and 4·8 per cent. respectively; the equivalent figure in the less productive Stud B, is 13·7 per cent.

7. Under Karroo conditions, prolific Merino stud ewes experience normal ovulation and oestrus as soon as 12 to 60 days after parturition, while in other instances this period is found to range between 111 and 134 days. Such short periods of sexual rest permit an easy conversion of the lambing season from autumn to spring and *vice versa*.

Further, evidence indicates that after longer periods of sexual rest, there appears to be no definite tendency for prolific ewes under Karroo conditions to adhere to any one particular time of the year or season for lambing.

8. It must be emphasized that the above analysis was made from the records of the most prolific ewes in the three stud registers, and that the average fertility of the studs is very likely to be somewhat lower than that reflected by this analysis.

Recommendations.—1. The infertility of maiden ewes reflected in the results of the analysis of the records of three Merino studs is marked.

The control or hand service method of mating maiden ewes is preferable to the small paddock system of mating, in that the former method reveals the cases in which sexual activity is absent and in which fertility has not been established by mating. Hence, controlled serving clearly indicates the need for the extension of the serving period in order to obtain a maximum number of successful matings.

When mating is undertaken in the spring, every endeavour should be made to autumn mate ewes which did not exhibit oestrus during the spring, or which were not fertilised during the spring mating.

The need for setting the generative organs of young sheep in motion appears to be of such great importance, that it may prove advantageous to extend the mating periods over severel months and to tolerate the disadvantages of awkward periods of lambing.

2. The breeding histories of the most prolific ewes in three Merino studs have been examined. The postponement of the breeding of maiden Merino ewes decreases the life period of lambing and reduces fertility and fecundity. Every endeavour should be made to obtain normal growth and to establish fertility by mating maiden ewes between the ages of 18 to 24 months. Recommendations for accomplishing this have been made in the above section.

The occurrence of non-lambing years means direct economic loss. Non-lambing years result in reduced material from which selection for improvement is to be made. This latter aspect is of particular importance in the progress of breeding in South Africa, where the studs are comparatively small and consequently selection is limited. Many factors may bring about infertility; the proper management of mating operations appears to be of considerable importance. However, the subject is of too great length to be dealt with fully here; the precautions necessary to ensure fertility were mentioned recently in a general discussion by Roux and Hoffman (1935).

As fertility has a genetic basis, selection for the character will bring about increased fertility. Mr. P. D. Rose (1935) in private correspondece with the author, drew attention to the greater need for attention to the milking qualities of ewes during the selection of breeding stock. The establishment of higher milking qualities would permit greater concentration upon selection for fecundity.

B. The Breeding Habits of Sheep in Various Parts of South Africa.

A certain amount of information relative to the breeding habits of sheep in South Africa has become available at a few centres where researches upon the sex physiology of sheep have been conducted. Only recently, experiments in sex physiology have been organized to study the peculiarities of various breeds of sheep and such differences as may result due to altered physiographical conditions. A small portion of this work has been reported in this thesis. (Experiments 6 and 7).

Küpfer (1928) states that, while sheep in Central Europe experience continuous annual sexual activity, Merino and Woolled Persian sheep in South Africa (western Free State) have a prolonged inactive or anoestrous period during the spring and summer months, thus limiting the period during which reproduction is possible.

Quinlan and Maré's (1931) observations on Merino sheep under Cape (Karroo) conditions, do not agree with those of Küpfer. The former authors state that, provided conditions (rainfall and pasture) are favourable, Merinos under South African conditions experience a continuous series of dioestrous cycles throughout the year.

The observations reported by the author in this thesis agree to a very great extent with the results of Küpfer (1928).

With the exception of the results reported by Küpfer (1928) on Woolled Persian sheep and those presented in this thesis on various crossbred sheep, no controlled observations upon the sexual activity of breeds other than the Merino have been recorded in South Africa.

The British breeds of sheep, in their home country and in other countries in the northern hemisphere, experience restricted annual sexual activity; the inactive sexual period, or anoestrum, occurs during the spring and summer months (Heape, 1900; Marshall 1903, 1922; Marshall and Hammond, 1925; Roberts, 1921; Cole and Miller, 1933; Grant, 1934).

Although, apparently, no controlled observations were made by Quinlan and Maré (1931), they are of the opinion that the acclimatisation of certain mutton breeds of sheep (Suffolk, Romney Marsh, Corriedale, Dorset Horn, and Wensleydale) takes about six months; the environmental change from Europe to South Africa is said to result in temporary sexual inactivity.

In order to obtain a general impression of the practical problems of sex physiology in sheep confronting stud breeders, a questionaire was circulated to many breeders of various breeds of sheep in the four provinces of the Union. Since failure to reproduce is due, in the great majority of cases, to the absence of sexual activity of the females, and the marked absence of breeding at times when mating is usually attempted (autumn and spring) is likely to be noticed by stud owners, the observations of stud breeders should yield some general information upon the breeding habits of their breeds of sheep. The main purpose of the questionaire was to ascertain, whether breeders had observed restricted or unrestricted season or seasons during which sheep would breed or mate. It is gratifying to note that many breeders replied to the questionaire, and that there appeared to be no hesitation in giving opinions based upon their experiences.

The non-woolled breeds such as the Blackhead Persian, Afrikander, and Karakul are restricted almost entirely to the semi-arid areas of the Union.

Blackhead Persian ewes reach sexual maturity at the age of 6 months, which is earlier than Merinos under similar conditions. It is considered that non-pregnant ewes of this breed may be bred at any time of the year; hence sexual activity is continuous throughout the year. It is possible to obtain two lambings in three years from this breed.

The Ronderib Afrikander reaches sexual maturity at 5 months and the ewes may be bred during the spring and autumn months.

Karakuls mate readily during the spring months and it is said that spring lambs are difficult to obtain. However, it is contended that two lambings a year are possible when the young lambs are slaughtered for pelts.

A limited number of studs of Corriedales and a few of the British breeds are found in the four provinces.

Suffolks have been found to have a restricted lambing season, which is said to extend, in the Transvaal, from July to September, and in the Cape, from July to November. Maiden ewes can be mated at the age of 18 months. An interesting case is reported in which imported ewes were landed in South Africa during November; they lambed the following April and May, and again in December of the same year; since then for many years, autumn lambing has been attempted without success. In another case, imported ewes were in this country for one year before they lambed and lambing occurred in the spring.

Southdowns have been experienced to have a restricted lambing season under Cape (Karroo) conditions; this season may extend from July to November. Maiden ewes may be bred successfully at the age of 18 months.

Oxfords in the western Transvaal can be bred to lamb in the autumn and spring. It is said that maiden ewes can be mated at 12 months of age.

Romney Marsh sheep have a restricted lambing season which occurs in the spring under Cape conditions. Maiden ewes can be mated successfully at the age of 18 months.

Dorset Horn sheep can be mated to lamb during the autumn months under Karroo conditions. No evidence of spring lambing in this breed is available.

Corriedales in the Transvaal have a restricted breeding season; lambs are born in the spring. A small stud of Corriedales is kept at the Ermelo Research Station, and it has not been possible to lamb down earlier than July. However, it has been reported that in Natal, Corriedales lamb in the autumn and spring seasons.

Merino breeders generally maintain that autumn lambing is more satisfactory in that such lambs do not receive the set back to which spring-born lambs are subject, because of internal parasitic infection. While many farmers mate only in the spring for autumn lambs, a large number obtain both autumn and spring born lambs; the practice is adopted in all four provinces. This would indicate the existence of two mating and, hence, two sexual seasons in Merinos under various South African conditions. It is important to note that, in cases where both autumn and spring lambs are obtained, it has been reported from some of the best sheep areas of the Cape (Karroo) and the Free State, that spring-born lambs are more easy to obtain than autumn-born lambs. This would indicate that, under those conditions, a larger number of ewes exhibit heat during the autumn than the spring, or that a larger percentage of ewes mated during the former season are fertilized. A certain number of breeders actually reported sexual inactivity of the ewes during the spring months.

Various explanations are given by breeders for the delayed sexual activity of Merino ewes. The greater percentage consider that rainfall is the determining factor; droughts delay the breeding season and ewes are said to come on heat about 14 days after the first good rains. Others can find no reason for the great variations in early and late mating seasons observed by them, and the failure of " dry " ewes to take the ram during certain seasons when it is desired to undertake mating operations.

Discussion.

It appears that the extreme degree of polyoestrum is a breed characteristic of some of the non-woolled breeds of sheep, especially the Blackhead Persian. While it is considered definite that the latter breed is capable of lambing at any time of the year under Cape (Karroo) conditions, it is not known whether continuous sexual activity would be maintained under different physiographical conditions.

Most British breeds of sheep when transferred to South Africa maintain their breed characteristic of restricted seasonal sexual activity, but they alter the rhythm with respect to the calendar months or, in other words, their sexual activity conforms to the new order of the seasons. It appears highly probable that the time taken for the conversion will depend upon the season during which the animals are introduced into the new environment, but it is suspected that the conversion is rapid.

The Dorset Horn, which is known to have two sexual seasons in other countries (Roberts, 1921; Marshall, 1922), apparently experiences similar activity under South African (Karroo) conditions.

With regard to the Merino, the bulk of evidence indicates that great variation exists. The extreme degree of polyoestrum has been observed under experimentation to exist under Cape (Karroo) conditions (Quinlan and Maré, 1931). No doubt, under such conditions, autumn and spring lambs are equally easy to obtain. The extreme polyoestrous condition apparently is a Merino characteristic. However, evidence indicates that the characteristic is not given full expression in all areas of the country. Whether, and to what degree, variations in the sexual activity of Merino sheep are influenced by climatic and nutritional conditions, will remain obscure until the problem is solved by strictly controlled experimentation.

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APPENDIX 2.

EXPERIMENT 2.

MACROSCOPIC EXAMINATION OF OVARIES.

[Groups I to VIII: Nos. (1) to (69).]

Group I.

Observations commenced 24th July, 1932.

Ration per capita per diem.—Maize, 4 oz.; teff hay, 2·5 lb.; lick *ad lib* (2 parts bone meal, 1 part salt).

(1) *Sheep No.* 29252.—Date slaughtered, 1st November, 1934; age, 4 years; condition, good; weight, 74·0 lb.

Sexual History.

27.7.32 to 15.8.32 (20 days): two exhibitions of oestrus.
16.8.32 to 13.2.33 (182 days): anoestrous period.
14.2.33 to 24.7.33 (161 days): ten exhibitions of oestrus.
25.7.33 to 22.2.34 (213 days): anoestrous period.
23.2.34 to 2.8.34 (161 days): ten exhibitions of oestrus.
3.8.34 to 1.11.34 (91 days): anoestrous period.

Uterus.—Weight, 22·5 gm.

Left Ovary.—Weight, 0·82 gm.; mesauresments, 1·3 by 1·3 by 0·9. cm.

The abnormally large measurement from the attached to the lateral border is due to the presence of a large Graafian follicle of 0·6 cm. in diameter. On section this Graafian follicle is found to contain a clear fluid, and the outer wall is thin. Eight small Graafian follicles of 0·1 to 0·2 cm. in diameter are present on the surface of the ovary.

No corpus luteum is seen. A few remnants of previous corpora lutea are present.

Right Ovary.—Weight, 0·63 gm.; measurements, 1·2 by 1·1 by 0·8 cm.

Six small Graafian follicles of 0·1 to 0·2 cm. are present.

No corpus luteum is seen.

No remnants of previous corpora lutea are present.

(2) *Sheep No.* 29270.—Date slaughtered, 15th August, 1934; age, 4 years; condition, fair; weight 61·0 lb.

Sexual History.

1.8.32 to 17.8.32 (17 days): two exhibitions of oestrus.
18.8.32 to 23.2.33 (190 days): anoestrous period.
24.2.33 to 22.7.33 (149 days): ten exhibitions of oestrus.
23.7.33 to 15.8.34 (389 days): anoestrous period.

No exhibition of oestrus was observed during the sexual season, February to August, 1934.

Left Ovary.—Weight, 0·70 gm.; measurements, 1·2 by 1·0 by 0·8 cm.

Two conspicuous Graafian follicles with diameters of 0·3 and 0·5 cm. are present together with several smaller ones of 0·1 to 0·2 cm. A total of six Graafian follicles can be counted.

No corpus luteum is present and no remnants of previous corpora lutea can be detected.

Right Ovary.—Weight, 0·56 gm.; measurements, 1·1 by 1·0 by 0·7 cm.

Eight Graafian follicles can be counted on the surface of the ovary; the three largest are 0·2 cm. in diameter.

There is no corpus luteum present. A slight yellowish colouration on the sectioned margin is the only indication of the presence of a remnant of a previous corpus luteum.

(3) *Sheep No.* 29325.—Date slaughtered, 4th January, 1935; age, 4 years; condition, fair; weight, 62·5 lb.

Sexual History.

24.7.32 to 14.3.33 (234 days): anoestrous period.
15.3.33 to 17.7.33 (125 days): six exhibitions of oestrus.
18.7.33 to 2.5.34 (289 days): anoestrous period.
3.5.34 to 7.8.34 (97 days): six exhibitions of oestrus.
8.8.34 to 4.1.35 (150 days): anoestrous period.

Uterus.—Weight, 20·5 gm.

Left Ovary.—Weight, 0·62 gm.; measurements, 1·5 by 1·2 by 0·7 cm.

Only four Graafian follicles can be seen on the surface of the ovary, the largest being 0·3 cm. However, on section eleven Graafian follicles can be counted; three of these are 0·3 and 0·2 cm. and the remainder 0·1 cm. and less in diameter.

No corpus luteum is present, but the remnants of four previous corpora lutea can be distinguished.

Right Ovary.—Weight, 0·63 gm.; measurements, 1·2 by 1·1 by 0·9 cm.

The Graafian follicles are very inconspicuous; three are detected, the largest of which is 0·3 cm. On section the latter is found to contain a clear fluid.

No corpus luteum is present, but the remnants of three previous corpora lutea are seen.

(4) *Sheep No.* 29328.—Date slaughtered, 7th September, 1934; age, 4 years; condition, poor; weight, 58·5 lb.

Sexual History.

24.7.32 to 21.2.33 (213 days): anoestrous period.
22.2.33 to 5.7.33 (134 days): nine exhibitions of oestrus.
6.7.33 to 13.3.34 (251 days): anoestrous period.
14.3.34 to 19.5.34 (67 days): three exhibitions of oestrus.
20.5.34 to 7.9.34 (111 days): anoestrous period.

Uterus.—Weight, 26·5 gm.

Left Ovary.—Weight, 0·58 gm.; measurements, 1·1 by 1·1 by 0·7 cm.

One large Graafian follicle is seen on the lateral border of the ovary; it measures 0·5 cm. in diameter and 0·3 cm. above the surface of the ovary. Two other Graafian follicles, measuring 0·2 and 0·3 cm. in diameter, are seen on the surface of the ovary. The largest Graafian follicle is found on section to contain a clear fluid.

No corpus luteum is present, but remnants of two previous corpora lutea are seen occurring as dark specks.

Right Ovary.—Weight, 0·66 gm.; measurements, 1·1 by 1·0 by 0·8 cm.

One Graafian follicle with a diameter of 0·3 cm. is seen while four of 0·1 cm. are also present.

No corpus luteum is present, but remnants of previous corpora lutea are seen, one occurring near the sectioned border of the ovary as a dark speck.

(5) *Sheep No.* 29340.—Date slaughtered, 7th September, 1934, age, 4 years; condition, good; weight, 80·5 lb.

Sexual History.

24.7.32 to 22.2.33 (214 days): anoestrous period.
23.2.33 to 31.5.33 (98 days): six exhibitions of oestrus.
1.6.33 to 8.2.34 (253 days): anoestrous period.
9.2.34 to 22.4.34 (73 days): two exhibitions of oestrus.
23.4.34 to 7.9.34 (138 days): anoestrous period.

Uterus.—Weight, 22·5 gm.

Left Ovary.—Weight, 0·56 gm.; measurements, 1·3 by 1·0 by 0·8 cm.

About ten Graafian follicles can be counted on the surface of the ovary, but on section fifteen are seen. The largest follicles measure 0·1 and 0·2 cm. in diameter.

No corpus luteum is present. Two remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 0·72 gm.; measurements, 1·3 by 1·1 by 0·8 cm.

Fifteen Graafian follicles can readily be counted; the three largest are 0·3 cm. in diameter and they are closely situated to one another.

No corpus luteum is present, but two remnants of previous corpora lutea can be seen.

(6) *Sheep No.* 29805.—Date slaughtered, 28th December, 1934; age, 4 years; condition, good; weight, 65·0 lb.

Sexual History.

24.7.32 to 14.2.33 (206 days): anoestrous period.
15.2.33 to 8.7.33 (144 days): nine exhibitions of oestrus.
9.7.33 to 1.3.34 (236 days): anoestrous period.
2.3.34 to 10.8.34 (162 days): ten exhibitions of oestrous.
11.8.34 to 28.12.34 (140 days): anoestrous period.

Uterus.—Weight, 30·5 gm.

Left Ovary.—Weight, 0·55 gm.; measurements, 1·2 by 1·1 by 0·8 cm.

Eleven small Graafian follicles are seen, the largest is 0·1 cm. in diameter.

No corpus luteum is present, but the remnants of two previous corpora lutea can be distinguished.

Right Ovary.—Weight, 0·65 gm.; measurements, 1·3 by 1·1 by 0·8 cm.

Eight Graafian follicles can be counted on the surface of the ovary. The largest follicle is situated on the pole of the ovary, measures 0·6 cm. in diameter, and is fairly prominent. On section this follicle is found to contain a clear fluid; its outer wall is thin, the inner lower surface is pinkish in colour, but the blood vessels are not prominent.

No corpus luteum is present, but two remnants of previous corpora lutea are seen.

(7) *Sheep No.* 29815.—Date slaughtered, 27th September, 1934; age, 4 years; condition, poor; weight, 48·0 lb.

Sexual History.

24.7.32 to 7.2.33 (199 days): anoestrous period.
8.2.33 to 27.6.33 (140 days): nine exhibitions of oestrus.
28.6.33 to 5.3.34 (251 days): anoestrous period.
6.3.34 to 19.6.34 (106 days): five exhibitions of oestrus.
20.6.34 to 27.9.34 (100 days): anoestrous period.

Uterus.—Weight, 15·5 gm.

Left Ovary.—Weight, 0·51 gm.; measurements, 1·2 by 1·0 by 0·8 cm.

Eight Graafian follicles are apparent on the surface of the ovary, the largest is 0·3 cm. in diameter and the remainder are 0·1 cm. The largest follicle is not prominent.

No corpus luteum is present. Three dark spots are seen on the surface of the ovary; on section these are found to be remnants of previous corpora lutea, being dark brown in colour and 0·1 cm. in diameter.

Right Ovary.—Weight, 0·38 gm.; measurements, 1·2 by 0·8 by 0·6 cm.

Seven small Graafian follicles, measuring 0·1 cm. and less, are apparent.

No corpus luteum is present. One dark brown remnant of a corpus luteum is seen; on section it is found to measure 0·05 cm.

(8) *Sheep No.* 32476.—Date slaughtered, 22nd September, 1934; age, 3½ years; condition, fair; weight, 60·0 lb.

Sexual History.

24.7.32 to 2.3.33 (222 days): anoestrous period.
3.3.33 to 15.7.33 (135 days): fixe exhibitions of oestrus.
16.7.33 to 5.6.34 (325 days): anoestrous period.
6.6.34 to 26.6.34 (21 days): two exhibitions of oestrus.
27.6.34 to 22.9.34 (88 days): anoestrous period.

Uterus.—Weight, 21·5 gm.

Left Ovary.—Weight, 0·54 gm.; measurements, 1·4 by 1·0 by 0·7 cm.

Graafian follicles are not very apparent on the surface of the ovary, but on section eleven are counted; these are all 0·1 cm. and less in diameter.

No corpus luteum is present. The remnants of two previous corpora lutea are seen on the surface of the ovary.

Right Ovary.—Weight, 0·40 gm.; measurements, 1·3 by 0·8 by 0·6 cm.

Only three Graafian follicles are seen after section of the ovary when it is held up to the light. The largest follicle is 0·3 cm. in diameter.

No corpus luteum is present, but one brown speck, the remnant of a previous corpus luteum, is seen near the sectioned margin of the ovary.

(9) *Sheep No.* 32491.—Date slaughtered, 4th January, 1935; age, 3½ years; condition, fair; weight, 64·5 lb.

Sexual History.

24.7.32 to 15.3.33 (235 days): anoestrous period.
16.3.33 to 12.5.33 (58 days): two exhibitions of oestrus.
13.5.33 to 5.5.34 (358 days): anoestrous period.
6.5.34 to 3.8.34 (90 days): three exhibitions of oestrus.
4.8.34 to 4.1.35 (154 days): anoestrous period.

Uterus.—Weight, 21·0 gm.

Left Ovary.—Weight, 0·50 gm.; measurements, 1·4 by 0·9 by 0·7 cm.

A large Graafian follicle with a thin outer wall is seen on the pole of the ovary; it measures 0·5 cm. in diameter, and when sectioned it is found to contain a clear fluid. A total of four follicles is seen.

No corpus luteum is present. Four remnants of previous corpora lutea are seen; on section two of these are found to be dark brown specks measuring 0·05 cm. and their margins are irregular.

Right Ovary.—Weight, 0·46 gm.; measurements, 1·3 by 0·95 by 0·75 cm.

Two Graafian follicles, 0·5 cm. in diameter, are situated in close proximity on one pole of the ovary. On section both these follicles are found to contain a clear fluid. A total of three follicles is seen.

No corpus luteum is present, but the remnants of three previous corpora lutea are present.

GROUP II.

Observations commenced 24th July, 1932.

Ration per capita per diem.—Maize, 4 oz.; teff hay, 2·5 lb.; lick *ad lib* (salt).

(10) *Sheep No.* 35508.—Date slauhtered, 1st November, 1934; age, 4 years; condition, good; weight, 67·0 lb.

Sexual History.

24.7.32 to 16.2.33 (208 days): anoestrous period.
17.2.33 to 10.7.33 (144 days): seven exhibitions of oestrus.
11.7.33 to 21.2.34 (226 days): anoestrous period.
22.2.34 to 1.8.34 (161 days): ten exhibitions of oestrus.
2.8.34 to 1.11.34 (92 days): anoestrous period.

Uterus.—Weight, 25·5 gm.

Left Ovary.—Weight, 0·78 gm.; measurements, 1·4 by 1·3 by 0·8 cm.

The external appearance of the ovary is irregular due to the presence of twelve Graafian follicles which are situated near the surface of the ovary and which are being pressed out to some extent by a corpus luteum situated adjacent to the largest follicle which has a diameter of 0·5 cm. On section the large follicle is found to contain a clear fluid and to have a thin outer wall.

The corpus luteum present projects only slightly above the surface of the ovary. On section it is found to be almost circular in form, its diameter being 0·5 cm. The substance of the corpus luteum is light yellow in colour and it has a depression measuring 0·2 cm. in its centre. This is undoubtedly a corpus luteum 1 at the end of the interoestrous period, so that it is apparent that ovulation occurred without the exhibition of oestrus as oestrus was last observed on 2nd August, 1934.

Right Ovary.—Weight, 0·66 gm.; measurements, 1·4 by 1·1 by 0·6 cm.

Twelve small Graafian follicles can be counted, the largest of which is 0·2 cm.

No corpus luteum is present, but two remnants of previous corpora lutea are seen occurring as dark specks.

(11) *Sheep No.* 35509.—Date slaughtered, 12th October, 1934; age, 4 years; condition, good; weight, 74·0 lb.

Sexual History.

24.7.32 to 13.1.33 (174 days): anoestrous period.
14.1.33 to 20.6.33 (158 days): nine exhibitions of oestrus.
21.6.33 to 17.1.34 (211 days): anoestrous period.
18.1.34 to 9.7.34 (174 days): eight exhibitions of oestrus.
10.7.34 to 12.10.34 (95 days): anoestrous period.

Uterus.—Weight, 18·5 gm.

Left Ovary.—Weight, 0·68 gm.; measurements, 1·2 by 1·2 by 0·8 cm.

Five Graafian follicles are apparent; the two largest measure 0·2 cm. One of the latter on section contains a clear fluid.

No corpus luteum is present. Five small yellowish specks representing the remains of previous corpora lutea are seen.

Right Ovary.—Weight, 0·51 gm.; measurements, 1·2 by 1·0 by 0·7 cm.

A Graafian follicle measuring 0·3 cm. is present on the lateral border of the ovary; it is fairly prominent and it gives the ovary an irregular shape. A few other follicles are seen on the surface of the ovary. On section the large follicle is found to contain a clear fluid and the outer wall is thin.

No corpus luteum is present, but four remnants of previous corpora lutea are seen and on section one is found to measure 0·1 cm.

(12) *Sheep No.* 29274.—Date slaughtered, 12th October, 1934; age, 4 years; condition, good; weight, 67·0 lb.

Sexual History.

24.7.32 to 15.8.32 (23 days): one exhibition of oestrus.
16.8.32 to 3.2.33 (172 days): anoestrous period.
4.2.33 to 29.8.33 (207 days): twelve exhibitions of oestrus.
30.8.33 to 15.4.34 (229 days): anoestrous period.
16.4.34 to 10.7.34 (86 days): three exhibitions of oestrus.
11.7.34 to 12.10.34 (94 days): anoestrous period.

Uterus.—Weight, 24·0 gm.

Left Ovary.—Weight, 0·49 gm.; measurements, 1·2 by 1·0 by 0·7. cm.

Seven Graafian follicles are seen in the ovary and most of these are apparent on the surface. All the follicles are small, none exceeding 0·1 cm. in diameter.

No corpus luteum is present. The remnants of five previous corpora lutea are seen occurring as dark specks on the surface of the ovary. On section the largest of these is seen to be dark brown in colour and it extends 0·15 cm. into the substance of the ovary.

Right Ovary.—Weight, 0·63 gm.; measurements, 1·4 by 1·0 by 0·8 cm.

One large Graafian follicle 0·6 cm. in diameter is seen; it is situated on the one pole of the ovary and projects 0·3 cm. above the surface of the ovary. On section this follicle is found to contain a clear fluid and its outer wall is thin.

No corpus luteum is present. Eleven remnants of previous corpora lutea can be counted on the surface of the ovary and on section some of these are found to be only 0·05 cm.

(13) *Sheep No.* 29279.—Date slaughtered, 15th August, 1934; age, 4 years; condition, fair; weight, 63·0 lb.

Sexual History.

24.7.32 to 6.3.33 (226 days): anoestrous period.
7.3.33 to 14.5.33 (69 days): five exhibitions of oestrus.
15.5.33 to 15.8.34 (458 days): anoestrous period.

No exhibition of oestrus was observed during the sexual season February to August, 1934.

Left Ovary.—Weight, 0·39 gm.; measurements, 0·9 by 0·8 by 0·6 cm.

Six Graafian follicles can be counted, the largest of which is 0·2 cm. in diameter. Two of the follicles when sectioned contain a clear fluid.

No corpus luteum is present, but one remnant of a previous corpus luteum is seen.

Right Ovary.—Weight, 0·42 gm.; measurements, 1·0 by 0·9 by 0·6 cm.

Numerous Graafian follicles are present in the ovary, the largest of which is 0·4 cm. The latter has been sectioned and is found to contain a clear fluid. There are at least four follicles about half the size of the largest follicle; the former are situated near the surface of the ovary.

No corpus luteum is present and no remnants of corpora lutea are seen.

(14) *Sheep No.* 29335.—Date slaughtered, 21st December, 1934; age, 4 years; condition, poor; weight, 44·0 lb.

Sexual History.

24.7.32 to 3.3.33 (223 days): anoestrous period.
4.3.33 to 19.7.33 (137 days): eight exhibitions of oestrus.
20.7.33 to 26.6.34 (342 days): anoestrous period.
27.6.34 to 31.7.34 (35 days): three exhibitions of oestrus.
1.8.34 to 21.12.34 (143 days): anoestrous period.

Uterus.—Weight, 15·5 gm.

Left Ovary.—Weight, 0·59 gm.; measurements, 1·4 by 1·0 by 0·8 cm.

Only three Graafian follicles of 0·2 cm. are seen in the ovary.

No corpus luteum is present, but two remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 0·74 gm.; measurements, 1·3 by 1·2 by 0·85 cm.

Several Graafian follicles can be seen on the surface of the ovary and on section eight follicles can be counted, the largest being 0·4 cm.

No corpus luteum is present, but five remnants of previous corpora lutea can be distinguished.

(15) *Sheep No.* 29341.—Date slaughtered, 28th December, 1934; age, 4 years; condition, fair; weight, 67·0 lb.

Sexual History.

24.7.32 to 4.3.33 (224 days): anoestrous period.
5.3.33 to 6.7.33 (124 days): five exhibitions of oestrus.
7.7.33 to 9.2.34 (218 days): anoestrous period.
10.2.34 to 17.7.34 (158 days): two exhibitions of oestrus.
18.7.34 to 28.12.34 (164 days): anoestrous period.

Uterus.—Weight, 40·0 gm.

Left Ovary.—Weight, 0·71 gm.; measurements, 1·4 by 1·3 by 0·8 cm.

Nine Graafian follicles can be counted, the largest of which is 0·2 cm.

The section through the ovary was made from the attached to the free border in order to section a corpus luteum which is situated near the attached border. The corpus luteum appears on the surface of the ovary as a pale prominence of 0·05 cm. above the surface and it measures 0·2 cm. across its top. On section the corpus luteum is found to measure 0·5 by 0·4 cm. The cut surface is a pale cream colour and there is a slightly darker line in the centre of the body. This is apparently a corpus luteum I. Four remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 0·66 gm.; measurements, 1·3 by 1·1 by 0·8 cm.

The surface of the ovary is somewhat irregular; on section this is found to be due to the presence of a large number of Graafian follicles, fifteen are counted, which are all situated near the surface of the ovary. However, all the follicles are small, the largest being 0·15 cm.

No corpus luteum is present, but the remnants of seven previous corpora lutea can be distinguished.

(16) *Sheep No.* 29793.—Date of slaughter, 28th December, 1934; age, 4 years; condition, fair; weight, 56·5 lb.

Sexual History.

34.7.32 to 5.3.33 (225 days): anoestrous period.
6.3.33 to 10.8.33 (158 days): ten exhibitions of oestrus.
11.8.33 to 10.3.34 (212 days): anoestrous period.
11.3.34 to 26.7.34 (138 days): seven exhibitions of oestrus.
27.7.34 to 28.12.34 (155): anoestrous period.

Uterus.—Weight, 36·5 gm.

Left Ovary.—Weight, 1·40 gm.; measurements, 1·5 by 1·2 by 1·6 cm.

The abnormal shape of the ovary is due to the presence of a large Graafian follicle and a corpus luteum which are situated on either side of the attached border of the ovary.

Seven Graafian follicles are counted, the largest of which is 0·5 cm.; it is being pushed out by the corpus luteum. The largest follicle on section is found to contain a clear fluid.

The corpus luteum has a very small projecting head, but it measures 0·2 cm. across the top. The head is somewhat lighter than the surrounding body, which is pinkish and on which small blood vessels can be seen. On section the corpus luteum is found to measure 1·2 by 1·0 cm.; it is pear-shaped. The cut surface is flesh-coloured and very slightly pink. A cavity, 0·5 by 0·4 cm., is present in the centre of the body and the cavity contains a fluid. This is apparently a corpus luteum I.

Right Ovary.—Weight, 0·58 gm.; measurements, 1·3 by 1·05 by 0·7 cm.

Ten Graafian follicles, all measuring 0·1 cm. and less, are present in the ovary.

No corpus luteum is present, four remnants of previous corpora lutea are seen as dark specks.

(17) *Sheep No.* 29827.—Date slaughtered, 28th December, 1934; age, 4 years; conditon, good; weight, 73·0 lb.

Sexual History.

24.7.32 to 17.2.33 (209 days): anoestrous period.
18.2.33 to 20.8.33 (184 days): ten exhibitions of oestrus.
21.8.33 to 3.4.34 (226 days): anoestrous period.
4.4.34 to 12.8.34 (131 days): six exhibitions of oestrus.
13.8.34 to 28.12.34 (138 days): anoestrous period.

Uterus.—Weight, 24·0 gm.

Left Ovary.—Weight, 0·64 gm.; measurement, 1·2 by 1·2 by 0·7 cm.

Ten Graafian follicles can be counted; the largest is 0·2 cm.

The ovary appears to bulge on the side of the free border, but no projection is present. However, on section, a corpus luteum, measuring 0·4 by 0·4 cm., is found. The body is light yellow in colour and its margins are not well defined. This is apparently a corpus luteum I in the latter part of the interovulation period.

Right Ovary.—Weight, 0·63 gm.; measurements, 1·1 by 1·1 by 0·8 cm.

On section of the ovary, fourteen Graafian follicles can be counted, the largest being 0·4 cm.

No corpus luteum is present, but two remnants of previous corpora lutea are seen.

(18) *Sheep No.* 32480.—Date slaughtered, 21st December, 1934; age, 3½ years; condition, fair; weight, 61·0 lb.

Sexual History.

24.7.32 to 7.3.33 (227 days): anoestrous period.
8.3.33 to 25.3.33 (18 days): two exhibitions of oestrous.
26.3.33 to 18.5.34 (419 days): anoestrous period.
19.5.34 to 28.7.34 (71 days): three exhibitions of oestrus.
29.7.34 to 21.12.34 (146 days): anoestrous period.

Uterus.—Weight, 27·5 gm.

Left Ovary.—Weight, 0·6 gm.; measurements, 1·1 by 0·9 by 0·75 cm.

Eleven Graafian follicles can be counted when the sectioned ovary is held up to the light, although only seven follicles are apparent on the surface of the ovary. The largest follicle on section is found to contain a clear fluid.

A slight prominence is seen on the surface of the ovary near the sectioned border. A section made through the prominence reveals it to be a corpus luteum, measuring 0·2 by 0·2 cm. The body is very pale, almost white in colour; it is probably a corpus luteum at the end of the interovulation period or a corpus luteum of the previous interovulation period.

Right Ovary.—Weight, 0·48 gm.; measurements, 1·2 by 0·9 by 0·7 cm.

Eight Graafian follicles can be counted, the largest of which is 0·5 cm. in diamter. The latter, on section, contains a clear fluid.

No corpus luteum is present, but the remnants of six previous corpora lutea are seen occurring as dark specks.

(19) *Sheep No.* 32493.—Date slaughtered, 21st December, 1934; age, 3½ years; condition, good; weight, 74·0 lb.

Sexual History.

24.7.32 to 28.3.33 (248 days): anoestrous period.
29.3.33 (1 day): one exhibition of oestrus.
30.3.33 to 6.5.34 (403 days): anoestrous period.
7.5.34 to 15.8.34 (101 days): five exhibitions of oestrus.
16.8.34 to 21.12.34 (128 days): anoestrous period.

Uterus.—Weight, 21·0 gm.

Left Ovary.—Weight, 0·54 gm.; measurements, 1·0 by 1·2 by 0·7 cm.

Two Graafian follicles, the larger of which is 0·5 cm., are situated on the free border of the ovary, giving it an abnormal shape. On section, the larger follicle is found to contain a clear fluid. The other follicle is found to be 0·3 cm. in diameter.

No corpus luteum is present, but the remnants of nine previous corpora lutea are distinguished.

Right Ovary.—Weight, 0·46 gm.; measurements, 1·2 by 1·0 by 0·65 cm.

Five very small Graafian follicles can be counted; they vary from 0·1 cm. and less in diameter.

No corpus luteum is present, but the remnants of four previous corpora lutea occur as dark specks.

GROUP III.

Observations commenced, 24th July, 1932.

Ration per capital per diem.—Maize, 2·7 oz.; cotton-seed meal, 1·3 oz.; teff hay, 2·5 lb.; lick, *ad lib.* (salt).

(20) *Sheep No.* 35499.—Date slaughtered, 7th September, 1934; age, 4 years; condition, fair; weight, 68·5 lb.

Sexual History.

24.7.32 to 7.2.33 (199 days): anoestrous period.
8.2.33 to 16.4.33 (68 days): three exhibitions of oestrus.
17.4.33 to 10.5.34 (389 days): anoestrous period.
11.5.34 (1 day): one exhibition of oestrus.
12.5.34 to 7.9.34 (119 days): anoestrous period.

Uterus.—Weight, 20·5 gm.

Left Ovary.—Weight, 0·89 gm.; measurements, 1·6 by 1·1 by 0·9 cm.

Six Graafian follicles can be counted; four are 0·2 cm. and the remainder 0·1 cm. in diameter.

No corpus luteum is present, but one remnant of a previous corpus luteum is seen.

Right Ovary.—Weight, 0·88 gm.; measurements, 1·5 by 1·1 by 0·7 cm.

Four Graafian follicles, 0·1 to 0·2 cm., are present in the ovary.

No corpus luteum is present, but a few remnants of previous corpora lutea are seen.

(21) *Sheep No.* 35498.—Date slaughtered, 23rd August, 1934; age, 4 years; condition, fair; weight, 57·0 lb.

Sexual History.

24.7.32 to 22.4.33 (273 days): anoestrous period.
23. 4.33 to 14.7.33 (83 days): three exhibitions of oestrus.
15.7.33 to 23.8.34 (405 days): anoestrous period.

No exhibition of oestrus was observed during the sexual season, February to August, 1934.

Uterus.—Weight, 18·5 gm.

Left Ovary.—Weight, 0·61 gm.; measurements, 1·2 by 1·1 by 0·1 cm.

A very large number of Graafian follicles of varying sizes are present in the ovary; a total of ten is counted. The ovary has an irregular shape and although the follicles are prominent, the largest follicle is only 0·3 cm. in diameter. Several follicles are 0·1 to 0·2 cm.

In close proximity to the largest follicle is a corpus luteum which when sectioned measures 0·2 cm. in diameter. It is a light yellow colour. It is apparently a corpus luteum I at the end of an interovulation period, or the corpus luteum of the previous interovulation period.

Right Ovary.—Weight, 0·42 gm.; measurements, 1·0 by 0·9 by 0·6 cm.

Two Graafian follicles can be seen on the surface of the ovary, but on section, four smaller follicles can be seen. The largest follicle is 0·2 cm.

A corpus luteum is not present, but a few dark specks indicate the remnants of previous corpora lutea.

(22) *Sheep No.* 29258.—Date slaughtered, 1st November, 1934; age, 4 years; condition, good; weight, 89·0 lb.

Sexual History.

24.7.32 to 2.3.33 (222 days): anoestrous period.
3.3.33 to 8.7.33 (128 days): six exhibitions of oestrus.
9.7.33 to 15.3.34 (250 days): anoestrous period.
16.3.34 to 19.7.34 (126 days): five exhibitions of oestrus.
20.7.34 to 1.11.34 (105 days): anoestrous period.

Uterus.—Weight, 23·5 gm.

Left Ovary.—Weight, 0·72 gm.; measurements, 1·4 by 1·2 by 0·7 cm.

Seven small Graafian follicles are counted; the largest measures 0·15 cm.

No corpus luteum is present, but a few remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 0·80 gm.; measurements, 1·4 by 1·2 by 1·0 cm.

The surface of the ovary is irregular, due to the presence of numerous Graafian follicles, two of which are 0·5 cm. On section, the latter follicles are found to contain a clear fluid.

No corpus luteum is present.

(23) *Sheep No.* 29265.—Date slaughtered, 1st November, 1934; age, 4 years; condition, fair; weight, 63·0 lb.

Sexual History.

24.7.32 to 20.2.33 (212 days): anoestrous period.
21.2.33 to 7.6.33 (107 days): four exhibitions of oestrous.
8.6.33 to 12.3.34 (278 days): anoestrous period.
13.3.34 to 28.6.34 (108 days): five exhibitions of oestrus.
29.6.34 to 12.10.34 (106 days): anoestrous period.

Uterus.—Weight, 27·5 gm.

Left Ovary.—Weight, 0·67 gm.; measurements, 1·2 by 1·1 by 0·7 cm.

Four Graafian follicles situated on the lateral border of the ovary give it an irregular shape. It is found, on section, that the largest follicles measure 0·5 and 0·3 cm. and that the more superficial follicles were being pressed out by several more deeply situated follicles.

No corpus luteum is present, but two remnants occurring as dark specks are seen.

Right Ovary.—Weight, 0·57 gm.; measurements, 1·2 by 0·9 by 0·8 cm.

Three Graafian follicles, the largest of which is 0·2 cm., are seen on the surface. On section, a few more smaller follicles are revealed.

No corpus luteum is present. Six remnants of previous corpora are counted and these are found to be 0·05 cm.

(24) *Sheep No.* 29273.—Date slaughtered, 14th September, 1934; age, 4 years; condition, poor; weight, 65·0 lb.

Sexual History.

24.7.32 to 13.2.33 (205 days): anoestrous period.
14.2.33 to 26.7.33 (163 days): nine exhibitions of oestrus.
27.7.33 to 10.5.34 (288 days): anoestrous period.
11.5.34 to 27.5.34 (17 days): two exhibitions of oestrus.
28.5.34 to 14.9.34 (110 days): anoestrous period.

Uterus.—Weight, 22·5 gm.

Left Ovary.—Weight, 0·68 gm.; measurements, 1·3 by 1·1 by 0·9 cm.

The presence of large Graafian follicles and a large number of follicles gives the ovary an irregular shape. The largest follicle is 0·6 cm. in diameter and it projects 0·2 cm. above the surface of the ovary. The next largest follicle is 0·4 cm. In addition, at least four follicles of 0·1 cm. can be distinguished on the surface of the ovary. On section, several more follicles become apparent. The largest follicle, on section, is found to contain a clear fluid.

No corpus luteum is present, but two remnants of previous corpora lutea are seen occurring as dark specks.

Right Ovary.—Weight, 0·55 gm.; measurements, 1·2 by 1·1 by 0·8 cm.

The largest Graafian follicle seen is 0·2 cm. and several of 0·1 cm. are present; a total of six follicles can be counted.

No corpus luteum is present, but a few remnants of previous corpora lutea are seen.

(25) *Sheep No.* 29283.—Date slaughtered, 7.9.34; age, 4 years; condition, good; weight, 73·0 lb.

Sexual History.

24.7.32 to 16.3.33 (236 days): anoestrous period.
17.3.33 to 15.6.33 (91 days): five exhibitions of oestrus.
16.6.33 to 29.3.34 (287 days): anoestrous period.
30.3.34 (1 day): one exhibition of oestrus.
31.3.34 to 7.9.34 (161 days): anoestrous period.

Uterus.—Weight, 19·5 gm.

Left Ovary.—Weight, 0·45 gm.; measurements, 1·2 by 1·1 by 0·7 cm.

Five Graafian follicles are apparent on the surface of the ovary. The largest follicle present in the ovary is 0·4 cm., the remainder are 0·1 to 0·2 cm. in diameter. The largest follicle has been sectioned and it contains a clear fluid.

No corpus luteum is present, but a few remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 0·52 gm.; measurements, 1·2 by 1·1 by 0·8 cm.

The ovary has an irregular appearance due to the prominence of three Graafian follicles. The largest follicle is 0·4 cm. and another is 0·3 cm. in diameter; they project 0·2 cm. above the surface of the ovary. Four smaller follicles are seen. The largest follicle has been sectioned; it contains a clear fluid, its outer wall is thin and small blood-vessels can be seen in the cavity.

A corpus luteum, measuring 0·2 by 0·4 cm., is present in the ovary and it has probably caused the follicles to project by pushing them out. The corpus luteum is not apparent on the surface of the ovary, but it is readily seen on section. It has a light outer margin; the centre is a deeper yellow and a slight depression occurs in the centre of the body. Some dark specks, the remnants of previous corpura lutea, are present.

(26) *Sheep No.* 29334.—Date slaughtered, 22nd September, 1934; Age, 4 years; condition, fair; weight, 58·0 lb.

Sexual History.

24.7.32 to 19.3.33 (239 days): anoestrous period.
20.3.33 to 27.5.33 (69 days): four exhibitions of oestrus.
28.5.33 to 9.4.34 (317 days): anoestrous period.
10.4.34 to 19.6.34 (71 days): four exhibitions of oestrus.
20.6.34 to 22.9.34 (95 days): anoestrous period.

Uterus.—Weight, 18·5 gm.

Left Ovary.—Weight, 0·52 gm.; measurements, 1·2 by 1·0 by 0·8 cm.

Seven Graafian follicles can be counted on the usrface of the ovary. The two largest follicles are 0·5 and 0·3 cm. in diameter; the latter was pressed out by the former to 0·1 cm. above the surface of the ovary.

No corpus luteum is present. On section a few brown specks with indefinite margins are seen; these are remnants of previous corpora lutea.

Right Ovary.—Weight, 0·38 gm; measurements, 1·1 by 0·9 by 0·8 cm.

No Graafian follicles are apparent on the surface of the ovary. However, on section seven follicles can be counted, the largest being 0·2 cm. The latter was sectioned and it contains a clear fluid.

No corpus luteum is present. One brown spot is seen on the surface of the ovary. On section it is found to be 0·1 cm.; it is obviously a remnant of a previous corporus luteum.

(27) *Sheep No.* 32482.—Date slaughtered, 1st November, 1934; age, 3½ years; condition, fair; weight, 65·0 lb.

Sexual History.

24.7.32 to 14.3.33 (234 days): anoestrous period.
15.3.33 (1 day): one exhibition of oestrus.
16.3.33 to 1.6.34 (443 days): anoeostrous period.
2.6.34 to 9.7.34 (38 days): two exhibitions of oestrus.
10.7.34 to 1.11.34 (115 days): anoestrous period.

Uterus.—Weight, 18·5 gm.

Left Ovary.—Weight, 0·63 gm.; measurements, 1·5 by 1·0 by 0·7 cm.

Eight Graafian follicles of diameters 0·1 to 0·2 cm. are counted on the surface of the ovary and on section two larger follicles of 0·3 cm. are seen.

No corpus luteum is present, but five remnants of previous corpora lutea are seen occurring as dark brown specks of 0·1 cm.

Right Ovary.—Weight. 0·48 gm.; measurements, 1·4 by 0·9 by 0·6 cm.

The Graafian follicles in the ovary are inconspicuous; on section four small follicles measuring 0·1 cm. are seen.

No corpus luteum is present, but three remnants of previous corpora lutea are seen and on section these are found to be brownish with indefinite margins and 0·1 cm. in diameter.

(28) *Sheep No.* 32495.—Date slaughtered, 27th October, 1934; age, 3½ years; condition, good; weight, 88·0 lb.

Sexual History.

24.7.32 to 12.3.33 (232 days): anoestrous period.
13.3.33 to 3.5.33 (52 days): three exhibitions of ooestrus.
4.5.33 to 11.4.34 (343 days): anoestrous period.
12.4.34 to 31.8.34 (142 days): six exhibitions of oestrus.
1.9.34 to 27.10.34 (57 days): anoestrous period.

Uterus.—Weight, 20·5 gm.

Left Ovary.—Weight, 0·48 gm.; measurements, 1·4 by 1·0 by 0·6 cm.

A large Graafian follicle 0·5 cm. in diameter is present on the one pole of the ovary, but the follicle is not prominent. It has been sectioned and it contains a clear fluid. Two small follicles are apparent in the substance of the ovary when the latter is held up to the light.

No corpus luteum is present, but two remnants of previous corpora lutea can be distinguished on the surface of the ovary.

Right Ovary.—Weight, 0·58 gm.; measurements, 1·4 by 1·1 by 0·7 cm.

Two Graafian follicles each 0·3 cm. in diameter can be seen; both have been sectioned and they contain a clear fluid.

No corpus luteum is present. Seven dark specks, the remnants of previous corpora lutea are seen; they vary in colour from yellow to dark brown, and the largest, which is dark brown, is 0·05 cm. in diameter.

GROUP IV.

Observations commenced 24th July, 1932.

Ration per capita per diem.—(*a*) 24th July, 1932, to 1st March, 1933: Maize, 4 oz.; teff hay, 2·5 lb.; Lick, *ad lib.* (2 parts bone meal, 1 part salt). (*b*) 2 nd March, 1933 to termination: Teff hay, 3·0 lb.; Lick, *ad lib* (2 parts bone meal, 1 part salt.

(29) *Sheep No.* 29261.—Date slaughtered, 30th August, 1934; age, 4 years; condition, poor; weight, 52·0 lb.

Sexual History.

24.7.32 to 23.2.33 (215 days): anoestrous period.
24.2.33 to 28.8.33 (186 days): twelve exhibitions of oestrus.
29.8.33 to 31.12.33 (125 days): anoestrous period.
1.1.34 to 7.2.34 (38 days): two exhibitions of oestrus.
8.2.34 to 30.8.34 (204 days): anoestrous period.

Uterus.—Weight, 19·5 gm.

Left Ovary.—Weight, 0·56 gm.; measurements, 1·2 by 1·1 by 0·7 cm.

Eight Graafian follicles can be counted in the ovary, the largest is 0·3 cm. in diameter; six of the follicles can be seen on the surface of the ovary.

No corpus luteum is present. The remnant of a corpus luteum measuring 0·1 cm. is seen.

Right Ovary.—Weight, 0·53 gm.; measurements, 1 3 by 0·9 by 0·7 cm.

Several Graafian follicles can be seen on the surface of the ovary, the largest is 0·3 cm. and there are many of 0·2 and 0·1 cm. None of the follicles are prominent. The large follicle on section is found to contain a clear fluid.

No corpus luteum is present and only one remnant of a previous corpus luteum can be found.

(30) *Sheep No.* 29268.—Date slaughtered, 4th October, 1934; age, 4 years; condition, fair; weight, 64·0 lb.

Sexual History.

24.7.32 to 19.1.33 (180 days): anoestrous period.
20.1.33 to 24.7.33 (186 days): ten exhibitions of oestrus.
25.7.33 to 4.4.34 (254 days): anoestrous period.
5.4.34 to 30 7.34 (117 days): five exhibitions of oestrus.
31.7.34 to 4.10.34 (66 days): anoestrous period.

Uterus.—Weight, 21·5 gm.

Left Ovary.—Weight, 0·67 gm.; measurements, 1·5 by 1·1 by 0·8 cm.

Ten Graafian follicles can be counted on the surface of the ovary, the largest being 0·3 cm. in diameter while the remainder are 0·2 and 0·1 cm. On section another follicle measuring 0·3 cm. is seen. Some of the follicles including one of the largest have been sectioned and they contain a clear fluid.

No corpus luteum is present, but the section of the ovary reveals a brownish spot 0·1 cm. just superior to a follicle; this is a remnant of a previous corpus luteum.

Right Ovary.—Weight, 0·50 gm.; measurements, 1·3 by 1·1 by 0·7 cm.

Seven small Graafian follicles each not exceeding 0·1 cm, are seen.

No corpus luteum is present, but one remnant of a previous corpus luteum has been cut through.

(31) *Sheep No.* 29298.—Date slaughtered, 4th October, 1934; age, 4 years; condition, fair; weight, 69·0 lb.

Sexual History.

24.7.32 to 30.1.33 (191 days): anoestrous period.
31.1.33 to 27.5.33 (117 days): six exhibition of oestrus.
28.5.33 to 5.5.34 (343 days): anoestrous period.
6.5.34 to 26.6.34 (52 days): four exhibitions of oestrus.
27.6.34 to 4.10.34 (100 days): anoestrous period.

Uterus.—Weight, 23·5 gm.

Left Ovary.—Weight, 0·44 gm.; measurements, 1·3 by 1·0 by 0·7 cm.

Eight Graafian follicles can be counted, the largest being 0·2 cm. in diameter.

No corpus luteum is present. One small speck 0·05 cm., a remnant of a previous corpus luteum, is seen on the sectioned margin of the ovary.

Right Ovary.—Weight, 0·72 gm.; measurements, 1·5 by 1·1 by 0·8 cm.

Ten Graafian follicles can be counted, the largest being 0·2 cm. in diameter.

No corpus luteum is present, but the remnants of three previous corpora lutea are seen. One dull dark brown spot is found to extend 0·2 cm. into the substance of the ovary.

(32) *Sheep No.* 29306.—Date slaughtered, 4th October, 1934; age, 4 years; condition, fair; weight, 64·5 lb.

Sexual History.

26.7.32 to 13.8.32 (19 days): two exhibitions of oestrus.
14.8.32 to 6.2.33 (177 days): anoestrous period.
7.2.33 to 28.8.33 (203 days): ten exhibitions of oestrus.
29.8.33 to 24 5.34 (269 days): anoestrous period.
25.5.34 to 1.7.34 (38 days): three exhibitions of oestrus.
2.7.34 to 4.10.34 (95 days): anoestrous period.

Uterus.—Weight, 19·5 gm.

Left Ovary.—Weight, 0·60 gm.; measurements, 1·3 by 1·2 by 0·8 cm.

Six Graafian follicles can be seen, the largest of which is 0·2 cm. in diameter.

No corpus luteum is present. Five dark spots are apparent on the surface of the ovary; these are the remnants of previous corpora lutea. Three of these bodies have been sectioined; they are 0·05 to 0·1 cm.; while two are of a lightish brown colour, one is somewhat darker.

Right Ovary.—Weight, 0·75 gm.; measurements, 1·5 by 1·1 by 0·8 cm.

Nine Graafian follicles can be counted, the largest being 0·2 cm. in diameter. The follicles cut through contain a clear fluid.

No corpus luteum is present. Four remnants of previous corpora lutea can be seen on the surface of the ovary; one has been sectioned; it is dark brown in colour and measures 0·1 cm.

(33) *Sheep No.* 29309.—Date slaughtered, 27th September, 1934; age, 4 years; condition, fair; weight, 62·5 lb.

Sexual History.

29.7.32 to 4.9.32 (38 days): three exhibitions of oestrus.
5.9.32 to 11.1.33 (129 days): anoestrous period.
12.5.32 to 28 7.33 (198 days): twelve exhibitions of oestrus.
29.7.33 to 27.4.34 (273 days): anoestrous period.
28.4.34 to 20.6.34 (54 days): four exhibitions of oestrus.
21.6.34 to 27.9.34 (99 days): anoestrous period.

Uterus.—Weight, 15·5 gm.

Left Ovary.—Weight, 0·62 gm.; measurements, 1·5 by 1·0 by 0·8 cm.

Ten small Graafian follicles can be counted; only one follicle is 0·2 cm., the remainder 0·1 cm. and less in diameter.

No corpus luteum is present, and no remnants of previous corpora lutea can be seen.

Right Ovary.—Weight, 0·88 gm.; measurements, 1·6 by 1·2 by 0·9 cm.

Nineteen Graafian follicles can be counted, all of which are small, the largest being 0·2 cm.

No corpus luteum is present, and only one remnant of a previous corpus luteum can be seen; the latter is a bright yellow spot and it measures 0·05 cm.

(34) *Sheep No.* 29316.—Date slaughtered, 22nd September, 1934; age, 4 years; condition, fair; weight, 69·0 lb.

Sexual History.

24.7.32 to 26.2.33 (218 days): anoestrous period.
27.2.33 to 21.7.33 (145 days): nine exhibitions of oestrus.
22.7.33 to 15.6.34 (329 days): anoestrous period.
16.6.34 (1 day): one exhibition of oestrus.
17.6.34 to 22.9.34 (98 days): anoestrous period.

Uterus.—Weight, 24·0 gm.

Left Ovary.—Weight, 0·58 gm.; measurements, 1·4 by 1·1 by 0·7 cm.

Graafian follicles are not easily seen on the surface of the ovary, but six follicles are seen on section of the ovary, the largest being 0·2 cm. in diameter. The latter follicle has been cut through and it contains a clear fluid.

No corpus luteum is present. Seven remnants of previous corpora lutea occurring as dark specks are seen.

Right Ovary.—Weight, 0·60 gm.; measurements, 1·5 by 1·1 by 0·7 cm.

There is one large Graafian follicle, 0·4 cm. in diameter which bulges very slightly above the surface of the ovary, while five follicles of 0·1 cm. are also present. The large follicle has been cut through; it contains a clear fluid and its outer wall is thin.

No corpus luteum is present. Seven remnants of previous corpora lutea are seen; they are 0·1 cm. in diameter.

(35) *Sheep No.* 29822.—Date slaughtered, 30th August, 1934; age, 4 years; condition, poor; weight, 50·0 lb.

Sexual History.

29.7.32 (1 day): one exhibition of oestrus.
30.7.32 to 28.1.33 (183 days): anoestrous period.
29.1.33 to 20.7.33 (173 days): nine exhibitions of oestrus.
21.7.33 to 30.8.34 (406 days): anoestrous period.

No exhibition of oestrus was observed during the sexual season February to August, 1934.

Uterus.—Weight, 16·0 gm.

Left Ovary.—Weight, 0·53 gm.; measurements, 1·2 by 0·9 by 0·7 cm.

Nine Graafian follicles are seen situated near the surface of the ovary; the largest follicle is 0·3 cm. in diameter; it is not prominant.

No corpus luteum is present, but several remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 0·53 gm.; measurements, 1·1 by 1·0 by 0·7 cm.

Two Graafian follicles of 0·2 cm. in diameter are seen on the surface of the ovary. On section, a follicle of 0·4 cm. is seen in addition to several small follicles varying in size.

No corpus luteum is present, but the remnants of previous corpora lutea are seen.

(36) *Sheep No.* 29825.—Date slaughtered, 14th September, 1934; age, 4 years; condition, fair; weight, 59·5 lb.

Sexual History.

24.7.32 to 21.2.33 (213 days): anoestrous period.
22.2.33 to 15.6.33 (114 days): six exhibitions of oestrus.
16.6.33 to 18.5.34 (337 days): anoestrous period.
19.5.34 (1 day): one exhibition of oestrus.
20.5.34 to 14.9.34 (118 days): anoestrous period.

Uterus.—Weight, 18·5 gm.

Left Ovary.—Weight, 0·46 gm.; measurements, 1·2 by 1·0 by 0·7 cm.

One Graafian follicle measuring 0·2 cm. is seen and three others of 0·1 cm. and less are present.

No corpus luteum is present, but six remnants of previous corpora lutea are seen as dark specks.

Right Ovary.—Weight, 0·64 gm.; measurements, 1·3 by 1·1 by 0·7 cm.

Very numerous small Graafian follicles can be seen on the surface of the ovary, and even more follicles are seen when the ovary is sectioned. A total of ten follicles is counted, the largest being 0·2 cm. in diameter.

No corpus luteum is present, and only one remnant of a previous corpus ulteum is seen.

(37) *Sheep No.* 35500.—Date slaughtered, 30th August, 1934; age, 4 years; condition, fair; weight, 66·0 lb.

Sexual History.

30.7.32 (1 day): one exhibition of oestrus.
31.7.32 to 27.1.33 (181 days): anoestrous period.
28.1.33 to 11.9.33 (227 days): twelve exhibitions of oestrus.
12.9.33 to 30.8.34 (353 days): anoestrous period.

No exhibition of oestrus was observed during the sexual season, February to August, 1934.

Uterus.—Weight, 17·5 gm.

Left Ovary.—Weight, 0·45 gm.; measurements, 1·1 by 0·9 by 0·6 cm.

One large Graafian follicle measuring 0·5 cm. is seen on the surface of the ovary and on section five small follicles 0·1 cm. are found. The large follicle has been sectioned and it contains a clear fluid.

No corpus luteum is present, but the remnants of some previous corpora lutea are seen.

Right Ovary.—Weight, 0·61 gm.; measurements, 1·2 by 1·0 by 0·7 cm.

A Graafian follicle measuring 0·4 cm. in diameter is readily seen on the surface of the ovary although it is not prominent. On section of the ovary, five smaller follicles 0·1 to 0·2 cm. are seen. The largest follicle has been cut through and it contains a clear fluid.

No corpus luteum is present, and only one remnant of a previous corpus luteum is seen.

Group V.

Observations commenced 22nd July, 1932.

Ration per capita per diem.—Maize, 5 oz.; teff hay, 2·5 lb.; Lick, *ad lib* (2 parts bone meal, 1 part salt).

(38) *Sheep No.* 35507.—Date slaughtered, 23rd August, 1934; age, aged; condition, fair; weight, 51·0 lb.

Sexual History.

22.7.32 (1 day): one exhibition of oestrus.
23.7.32 to 21.11.32 (122 days): anoestrous period.
22.11.32 to 6.9.33 (289 days): fourteen exhibitions of oestrus.
7.9.33 to 23.8.34 (351 days): anoestrous period.

No exhibition of oestrus was observed during the sexual season, February to August, 1934.

Uterus.—Weight, 32·0 gm.

Left Ovary.—Weight, 0·64 gm.; measurements, 1·4 by 1·1 by 0·6 cm.

Graafian follicles are very inconspicuous on the surface of the ovary, but on section four small follicles 0·1 cm. in diameter are seen.

No corpus luteum is present, but the remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 0·53 gm.; measurements (omitted).

One Graafian follicle, 0·3 cm. is seen near the surface of the ovary; this has been sectioned and it contains a clear fluid. On section of the ovary three more follicles 0·1 cm. in diameter are seen.

No corpus luteum is present, but the remnants of several previous corpora lutea are seen.

(39) *Sheep No.* 35506.—Date slaughtered, 14th December, 1934; age, 6 years; condition, fair; weight, 61·0 lb.

Sexual History.

9.7.32 to 29.8.32 (52 days): four exhibitions of oestrus.
30.8.32 to 22.11.32 (58 days): anoestrous period.
23.11.32 to 3.8.33 (255 days): eleven exhibitions of oestrus.
4.8.33 to 26.3.34 (235 days): anoestrous period.
27.3.34 to 27.8.34 (155 days): eight exhibitions of oestrus.
28.8.34 to 14.12.34 (109 days): anoestrous period.

Uterus.—Weight, 40·0 gm.

Left Ovary.—Weight, 1·13 gm.; measurements, 1·8 by 1·4 by 0·8 cm.

Twelve Graafian follicles are seen, the largest of which is 0·1 cm; many of the follicles are hardly visible. However, on section larger follicles are seen to be situated deeper in the tissues of the ovary: one is 0·4 cm. and two are 0·25 cm. in diameter.

No corpus luteum is present and no remnants of corpora lutea are seen.

Right Ovary.—Weight, 1·22 gm.; measurements, 1·8 by 1·5 by 0·9 cm.

Ten Graafian follicles can be counted, the largest of which is 0·15 cm. A projection of 0·2 cm. on one pole of the ovary proved, on section, to be a follicle which has been pushed out; it measures only 0·3 cm. and its outer wall is thick. The largest follicle seen is 0·4 cm.

No corpus luteum or remnants of corpora lutea are seen.

(40) *Sheep No.* 15239.—Date slaughtered, 23rd August, 1934; age, 6-7 years; condition, good; weight, 74·0 lb.

Sexual History.

26.7.32 (1 day): one exhibition of oestrus.
27.7.32 to 21.2.33 (210 days): anoestrous period.
22.2.33 to 8.7.33 (137 days): nine exhibitions of oestrus.
9.7.33 to 23.8.34 (411 days): anoestrous period.

No exhibition of oestrus was observed during the sexual season, February to August, 1934.

Uterus.—Weight, 50·5 gm.

Left Ovary.—Weight, 0·66 gm.; measurements, 1·5 by 1·0 by 0·6 cm.

Graafian follicles are not very apparent on the surface of the ovary, but two follicles of 0·1 cm. are seen when the ovary is sectioned.

A corpus luteum just appearing on the surface of the ovary measures 0·2 by 0·3 cm. It apparently is a receding corpus at a late stage. A few remnants of previous corpora lutea are present.

Right Ovary.—Weight, 0·80 gm.; measurements, 1·4 by 1·2 by 0·8 cm.

Numerous Graafian follicles are seen on the surface of the ovary; one although 0·5 cm. in diameter does not project above the surface of the ovary.

Near the sectioned margin of the ovary is a corpus luteum measuring 0·2 cm. in diameter. This corpus luteum also appears to be in a late receding stage. No remnants of previous corpora lutea seen.

(41) *Sheep No.* 21658.—Date slaughtered, 7th December, 1934; age, 6 years; condition, good; weight, 81·0 lb.

Sexual History.

9.7.32 to 15.9.32 (70 days): five exhibitions of oestrus.
16.9.32 to 12.3.33 (178 days): anoestrous period.
13.3.33 to 8.9.33 (180 days): twelve exhibitions of oestrus.
9.9.33 to 6.5.34 (241 days): anoestrous period.
7.5.34 to 16.10.34 (163 days): eleven exhibitions of oestrus.
17.10.34 to 7.12.34 (52 days): anoestrous period.

Uterus.—Weight, 34·5 gm.

Left Ovary.—Weight, 0·90 gm.; measurements, 1·6 by 1·2 by 0·7 cm.

Twelve Graafian follicles can be counted in the ovary, many of which are apparent on the surface of the ovary. The largest follicle is 0·3 cm. in diameter.

No corpus luteum is present, but the remnants of six previous corpora lutea are seen occurring as light brown specks.

Right Ovary.—Weight, 0·93 gm.; measurements, 1·6 by 1·2 by 0·9 cm.

Seven Graafian follicles can be counted, the largest of which is 0·5 cm. in diameter.

No corpus luteum is present although the remnants of ten previous corpora lutea are seen.

(42) *Sheep No.* 25876.—Date slaughtered, 14th December, 1934; age, 6 years; condition, fair; weight, 58·0 lb.

Sexual History.

17.7.32 (1 day): one exhibition of oestrus.
18.7.32 to 2.1.33 (169 days): anoestrous period.
3.1.33 to 14.7.33 (193 days): nine exhibitions of oestrus.
15.7.33 to 11.3.34 (240 days): anoestrous period.
12.3.34 to 11.7.34 (62 days): seven exhibitions of oestrus.
12.7.34 to 14.12.34 (156 days): anoestrous period.

Uterus.—Weight, 27·0 gm.

Left Ovary.—Weight, 0·65 gm.; measurements, 1·5 by 1·1 by 0·75 cm.

Fourteen Graafian follicles can be counted on the surface of the ovary, they are all 0·1 cm. and less in size. On section follicles are found throughout the tissues of the ovary; the largest seen is 0·2 cm. in diameter.

No corpus luteum is present, but five remnants of previous corpora lutea are seen; one of the latter when sectioned is found to be a dark brown irregular spot of 0·1 cm.

Right Ovary.—Weight, 0·85 gm.; measurements, 1·5 by 1·3 by 0·8 cm.

Fifteen Graafian follicles can be counted, the largest of which is 0·2 cm. On section follicles are found to exist throughout the tissue of the ovary and even near the attached border.

No corpus luteum is present, but seven remnants of previous corpora lutea are seen.

(43) *Sheep No.* 25883.—Date slaughtered, 22nd September, 1934; age, 6 years; condition, poor; weight, 53·0 lb.

Sexual History.

22.7.32 to 27.8.32 (37 days): three exhibitions of oestrus.
28.8.32 to 3.11.32 (68 days): anoestrous period.
4.11.32 to 24.7.33 (263 days): ten exhibition of oestrus.
25.7.33 to 18.1.34 (178) days): anoestrous period.
19.1.34 to 13.6.34 (146 days): two exhibitions of oestrus.
14.6.34 to 22.9.34 (101 days): anoestrous period.

Uterus.—Weight, 32·5 gm.

Left Ovary.—Weight, 0·58 gm.; measurements, 1·3 by 1·1 by 0·7 cm.

One Graafian follicle 0·3 cm. in diameter is seen but it is not prominent; numerous other follicles 0·1 cm. are seen on the surface of the ovary. On section twelve follicles can be counted.

No corpus luteum is present. A few remnants of previous corpora lutea are seen as dark specks; one of these has been sectioned and is 0·1 cm.

Right Ovary.—Weight, 0·60 gm.; measurements, 1·3 by 1·1 by 0·8 cm.

One Graafian follicle only 0·2 cm. in diameter is seen projecting 0·1 cm above the surface of the ovary, and several other follicles of 0·1 cm. are present . On section it is found that the projecting follicle had been pressed out by a larger follicle, 0·6 cm. in diameter, which is situated deeper in the tissues of the ovary.

No corpus luteum is present, but about six dark specks can be counted; the latter are remnants of previous corpora lutea.

(44) *Sheep No.* 25907.—Date slaughtered, 30th November, 1934; age, 7 years; condition, poor; weight, 53·0 lb.

Sexual History.

23.7.32 to 10.8.32 (19 days): two exhibitions of oestrus.
11.8.32 to 14.2.33 (188 days): anoestrous period.
15.2.33 to 20.8.33 (187 days): nine exhibitions of oestrus.
21.8.33 to 7.4.34 (230 days): anoestrous period.
8.4.34 to 9.10.34 (185 days): nine exhibitions of oestrus.
10.10.34 to 30.11.34 (52 days): anoestrous period.

Uterus.—Weight, 34·5 gm.

Left Ovary.—Weight, 0·51 gm.; measurements, 1·1 by 1·2 by 0·6 cm.

Three Graafian follicles are seen on the surface of the ovary, each of them being 0·1 cm.

No corpus luteum is present. The ovary bulges somewhat on its lateral border. A dark brown speck 0·075 cm. is seen on the top of the bulge. On section the spot is found to be a remnant of a corpus luteum; it measures 0·1 by 0·1 cm. and is dark brown in colour. Other remnants, light brown in colour, occur in close proximity.

Right Ovary.—Weight, 0·42 gm.; measurements, 0·9 by 1·1 by 0·6 cm.

Four Graafian follicles are seen; one measures 0·5 cm. and the remainder 0·1 cm. One of the smaller follicles is superimposed on the large follicle, giving the ovary an abnormal shape.

No corpus luteum is present, but a few remnants of previous corpora lutea are seen.

GROUP VI.

Observations commenced 7th October, 1932.

Treatment.—On grazing; lick, *ad lib.* (2 parts bone meal and 1 part salt).

(45) *Sheep No.* 15257.—Date slaughtered, 9th November, 1934; age, 6 years; condition, fair; weight, 75·0 lb.

Sexual History.

7.10.32 to 21.2.33 (138 days): anoestrous period.
22.2.33 to 1.9.33 (192 days): eleven exhibitions of oestrus.
2.9.33 to 28.12.33 (188 days): anoestrous period.
29.12.33 to 10.8.34 (225 days): ten exhibitions of oestrus.
11.8.34 to 9.11.34 (91 days): anoestrous period.

Uterus.—Weight, 48·0 gm.

Left Ovary.—Weight, 1·66 gm.; measurements, 2·2 by 1·4 by 0·9 cm.

The ovary is seen to contain one Graafian follicle 0·4 cm. in diameter and six follicles of 0·1 cm.

A very prominent corpus luteum is present. It projects 0·4 cm. above the surface of the ovary and it measures 0·9 cm. across the top or head. The head is circular, it is flattened on top and has a very slight depression in its centre. The head is pinkish in colour. On section the corpus luteum is found to occupy fully half of the ovary; the former measures 1·2 by 1·1 cm. it is pinkish in colour, and it has no central depression.

Right Ovary.—Weight, 0·69 gm.; measurements, 1·5 by 1·2 by 0·8 cm.

Eight Graafian follicles can be counted, the largest being 0·3 cm. in diameter. The latter has been sectioned and it contains a clear fluid.

No corpus luteum is present, but the remnants of six previous corpora lutea are seen.

(46) *Sheep No.* 15327.—Date slaughtered, 11th January, 1935; age, 7 years; condition, fair; weight, 63·5 lb.

Sexual History.

7.10.32 to 12.3.33 (157 days): anoestrous period.
13.3.33 to 10.8.33 (151 days): seven exhibitions of oestrus.
11.8.33 to 3.2.34 (177 days): anoestrous period.
4.2.34 to 5.8.34 (183 days): six exhibitions of oestrus.
6.8.34 to 11.1.35 (159 days): anoestrous period.

Uterus.—Weight, 60·5 gm.

Left Ovary.—Weight, 1·93 gm.; measurements, 1·8 by 1·9 by 1·1 cm.

The abnormal shape of the ovary is due to the presence of a large corpus luteum.

Six Graafian follicles can be counted in the ovary, the largest is 0·4 cm. The largest follicle has been sectioned; it contains a clear fluid and its outer wall is thin and transparent.

The corpus luteum does not have a projecting head, but its outer surface is pink in colour and a number of blood vessels can be seen transversing its surface. On section the corpus luteum is found to measure 1·2 by 1·1 cm. The cut surface is flesh coloured, and there is a cavity of 0·4 cm. in diameter which contains a fluid. This is apparently a corpus luteum I. Seven remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 1·03 gm.; measurements, 1·5 by 1·5 by 0·7 cm.

The ovary has a shrivelled appearance. Fifteen Graafian follicles can be counted in the ovary all of which are 0·1 cm. and less in diameter.

No corpus luteum is present, and only one remnant of a previous corpus luteum can be seen.

(47) *Sheep No.* 21504.—Date slaughtered, 11th January, 1935; age, 7 years; condition, poor; weight, 57·0 lb.

Sexual History.

7.10.32 to 8.2.33 (125 days): anoestrous period.
9.2.33 to 6.6.33 (118 days): five exhibitions of oestrus.
7.6.33 to 13.5.34 (341 days): anoestrous period.
14.5.34 to 23.8.34 (102 days): five exhibitions of oestrus.
24.8.34 to 11.1.35 (141 days): anoestrous period.

Uterus.—Weight, 35·5 gm.

Left Ovary.—Weight, 0·75 gm.; measurements, 1·5 by 1·1 by 0·8 cm.

Ten Graafian follicles can be counted on the surface of the ovary, the largest being 0·15 cm. However, on section of the ovary, a follicle measuring 0·5 cm. is found deeply situated in the substance of the ovary.

A projection of 0·1 cm. and measuring 0·3 cm. across its head is found on the surface of the ovary. It is pale and almost white in colour. On section it is found to be a corpus luteum measuring 0·6 by 0·6 cm. It has a central depression of 0·3 cm. and its cut surface is light flesh coloured. This is apparntly a corpus luteum I. No remnants of previous corpora lutea are present.

Right Ovary.—Weight, 0·48 gm.; measurements, 1·1 by 1·1 by 0·7 cm.

On section of the ovary eleven Graafian follicles can be counted, although eight are apparent on the surface of the ovary. The largest follicle is 0·3 cm. in diameter; it is deeply situated and it is surrounded by several other follicles.

No corpus luteum is present and no remnants of previous corpora luta are seen.

(48) *Sheep No.* 24928.—Date slaughtered, 22nd November, 1934; age, 7 years; condition, fair; weight, 72·0 lb.

Sexual History.

7.10.32 to 27.2.33 (144 days): anoestrous period.
28.2.33 to 5.8.33 (159 days): ten exhibitions of oestrus.
6.8.33 to 7.2.34 (186 days): anoestrous period.
8.2.34 to 25.9.34 (230 days): twelve exhibitions of oestrus.
26.9.34 to 22.11.34 (68 days): anoestrous period.

Uterus.—Weight, 45·0 gm.

Left Ovary.—Weight, 1·35 gm.; measurements, 1·9 by 1·4 by 0·9 cm.

Five Graafian follicles can be counted on the surface of the ovary, the largest being 0·2 cm. The ovary is soft and flabby and difficult to section. On section a follicle measuring 0·7 cm. is found lying deep in the parenchymatous layer. This follicle has been cut into and it contains a clear fluid.

No corpus lutum is present, but seventeen remnants of previous corpora lutea can be counted; the latter vary from light to dark brown in colour.

Right Ovary.—Weight, 1·2 gm.; measurements, 1·8 by 1·4 by 0·8 cm.

Eleven Graafian follicles can be counted in the ovary; the two largest follicles measure 0·3 cm. and they were found in close proximity.

No corpus luteum is present, but the remnants of six previous corpora lutea are seen.

(49) *Sheep No.* 25873.—Date slaughtered, 11th January, 1935; age, 6 years; condition, good; weight, 80·0 lb.

Sexual History.

7.10.32 to 3.3.33 (148 days): anoestrous period.
4.3.33 to 12.8.33 (162 days): nine exhibitions of oestrus.
13.8.33 to 16.2.34 (188 days): anoestrus period.
17.2.34 to 27.7.34 (161 days): ten exhibitions of oestrus.
28.7.34 to 11.1.35 (168 days): anoestrous period.

Uterus.—Weight, 41·5 gm.

Left Ovary.—Weight, 0·79 gm.; measurements, 1·5 by 1·3 by 0·8 cm.

Seven Graafian follicles can be seen in the ovary all of which are 0·1 cm. and less in diameter.

A very small projection is found on the surface of the ovary. On section of the ovary a corpus luteum is found measuring 0·3 by 0·3 cm. and the cut surfaces of the body are very pale. It is apparently a corpus luteum 1 during the latter part of the interovulation period. Nine remnants of previous corpora lutea are present.

Right Ovary.—Weight, 1·15 gm.; measurements, 1·6 by 1·5 by 0·9 cm.

Fifteen Graafian follicles can be counted in the ovary; there is one follicle of 0·3 cm. and three of 0·2 cm. Some follicles were cut through when the ovary was sectioned; they contained a clear fluid..

No corpus luteum is present, but the remnants of four corpora lutea are seen.

(50) *Sheep No.* 35501.—Date slaughtered, 14th December, 1934; age 7 years; condition, very good; weight, 84·0 lb.

Sexual History.

7.10.32 to 9.2.33 (126 days): anoestrous period.
10.2.33 to 27.5.33 (107 days): seven exhibitions of oestrus.
28.5.33 to 6.3.34 (283 days): anoestrous period.
7.3.34 to 4.9.34 (182 days): ten exhibitions of oestrus.
5.9.34 to 14.12.34 (101 days): anoestrous period.

Uterus.—Weight, 37·5 gm.

Left Ovary.—Weight, 0·81 gm.; measurements, 1·5 by 1·5 by 0·9 cm.

Five Graafian follicles can be counted, one of which is 0·55 cm. and the remainder very small. The largest follicle is prominent and the outer wall is transparent; it was cut into when the ovary was sectioned and it is found to contain a clear fluid.

A corpus luteum is present. It projects only 0·05 cm. above the surface of the ovary, the head measures 0·1 cm. acros its width. The colour is pale and it has a light yellow spot in its centre. On section the corpus luteum is found to be pale in colour; it measures 0·6 by 0·5 cm. It is apparently a corpus luteum I.

Right Ovary.—Weight, 0·48 gm.; measurements, 1·4 by 0·9 by 0·6 cm.

Only three Graafian follicles can be detected. The largest follicle is seen on section of the ovary; it measures 0·2 cm.

No corpus luteum is present, but the remnants of six previous corpora lutea are seen occurring as dark specks.

(51) *Sheep No.* 35496.—Date slaughtered, 30th November, 1934; age, 7 years; condition, very good; weight, 87·0 lb.

Sexual History.

7.10.32 to 23.2.33 (140 days): anoestrous period.
24.2.33 to 16.7.33 (143 days): nine exhibitions of oestrus.
17.7.33 to 17.2.34 (216 days): anoestrous period.
18.2.34 to 3.9.34 (197 days): twelve exhibitions of oestrus.
4.9.34 to 30.11.34 (88 days): anoestrous period.

Uterus.—Weight, 20·5 gm.

Left Ovary.—Weight, 0·56 gm.; measurements, 1·3 by 1·0 by 0·7 cm.

Four Graafian follicles can be seen on the surface of the ovary; they are not easily seen and the largest is 0·3 cm. The latter follicle has been cut into and it contains a clear fluid.

No corpus luteum is present, but the remnants of nine previous corpora lutea are seen.

Right Ovary.—Weight, 0·61 gm.; measurements, 1·4 by 1·0 by 0·7 cm.

Three Graafian follicles can be seen on the surface of the ovary and three more have become apparent on section of the ovary. The largest follicle occurs on the one pole of the ovary; it measures 0·5 cm. and when cut is found to contain a clear liquid.

No corpus luteum is present, but the remnants of five previous corpora lutea are seen.

(52) *Sheep No.* 35502.—Date slaughtered, 11th January, 1935; age, 6 years; condition, poor; weight, 68·0 lb.

Sexual History.

7.10.32 to 22.2.33 (139 days): anoestrous period.
23.2.33 to 1.8.33 (160 days): ten exhibitions of oestrus.
2.8.33 to 22.2.34 (205 days): anoestrous period.
23.2.34 to 27.6.34 (125 days): eight exhibitions of oestrus.
28.6.34 to 11.1.35 (198 days): anoestrous period.

Uterus.—Weight, 33·5 gm.

Left Ovary.—Weight, 0·93 gm.; measurements, 1·4 by 1·3 by 1·0 cm.

Fourteen Graafian follicles can be counted on the surface of the ovary; the largest follicle is 0·5 cm. However, when the ovary is sectioned twenty-four follicles are counted. The largest follicle has been cut into; it contains a clear fluid and its internal surfaces are pinkish.

No corpus luteum is present and three remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 0·72 gm.; measurements, 1·3 by 1·1 by 0·8 cm.

The Graafian follicles present in the ovary are all small, not exceeding 0·1 cm. in diameter. On section of the ovary seven follicles can be counted.

No corpus luteum is present, but four remnants of previous corpora lutea are seen.

(53) *Sheep No.* 35497.—Date slaughtered, 30th November, 1934; age, 7 years; condition, good; weight, 95·0 lb.

Sexual History.

7.10.32 to 14.2.33 (131 days): anoestrous period.
15.2.33 to 29.8.33 (196 days): ten exhibitions of oestrus.
30.8.33 to 2.1.34 (126 days): anoestrous period.
3.1.34 to 3.9.34 (244 days): ten exhibitions of oestrus.
4.9.34 to 30.11.34 (88 days): anoestrous period.

Uterus.—Weight, 29·5 gm.

Left Ovary.—Weight, 0·65 gm.; measurements, 1·5 by 1·1 by 0·7 cm.

Eight Graafian follicles can be counted on the surface of the ovary; the largest follicle is 0·4 cm. and the remainder are 0·1 cm. in diameter.

No corpus luteum is present but four remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 0·69 gm.; measurements, 1·2 by 1·2 by 0·9 cm.

Four Graafian follicles can be seen on the surface of the ovary; the largest follicle is 0·6 cm. and the remainder are 0·1 cm. in diameter. The largest follicle is found to bulge 0·15 cm. beyond the surface of the ovary. On section, it is found that this follicle is situated above another follicle of approximately the same size which was pressing the former out.

No corpus luteum is present, but a few remnants of previous corpora lutea are seen.

GROUP VII.

Observations commenced 7th October, 1932.

Treatment.—On grazing: Maize, 8 to 12 oz. per capita per diem; lick, *ad lib.* (2 parts bone meal, 1 part salt).

(54) *Sheep No.* 15351.—Date slaughtered, 30th November, 1934; age, 7 years; condition, good; weight, 84·0 lb.

Sexual History.

7.10.32 to 5.2.33 (122 days): anoestrous period.
6.2.33 to 31.8.33 (207 days): thirteen exhibitions of oestrus.
1.9.33 to 11.1.34 (133 days): anoestrous period.
12.1.34 to 29.10.34 (291 days): eighteen exhibitions of oestrus.
30.10.34 to 30.11.34 (32 days): anoestrous period.

Uterus.—Weight, 52·5 gm.

Left Ovary.—Weight, 0·72 gm.; measurements, 1·3 by 1·2 by 0·9 cm.

Two very inconspicuous small Graafian follicles are seen on the surface of the ovary, but on section of the ovary six small follicles are found to be present. A slight projection of 0·1 cm. above the surface of the ovary is found. It is marked with a series of concentric circles of small blood vessels which leave a small clear space in the centre. The projection measures 0·3 cm. across. When the area adjacent to the projection is touched with a pin, the projection bulges outward and it appears to enclose a liquid. When the pressure is realised, the projection returns to its original size. This is a Graakan follicle shortly before rupture.

No corpus luteum is present but a few remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 0·60 gm.; measurements, 1·4 by 1·0 by 0·7 cm.

Two Graafian follicles can be seen; the larger follicle is 0·3 cm. and when cut through it contains a clear fluid.

No corpus luteum is present, but the remnants of four previous corpora lutea are seen.

(55) *Sheep No.* 22210.—Date slaughtered, 16th November, 1934; age, 6 years; condition, good; weight, 75·0 lb.

Sexual History.

7.10.32 to 2.3.33 (147 days): anoestrous period.
3.3.33 to 30.7.33 (150 days): seven exhibitions of oestrus.
31.7.33 to 9.3.34 (222 days): anoestrous period.
10.3.34 to 11.9.34 (186 days): five exhibitions of oestrus.
12.9.34 to 16.11.34 (66 days): anoestrous period.

Uterus.—Weight, 31·5 gm.

Left Ovary.—Weight, 1·2 gm.; measurements, 1·4 by 1·5 by 0·9 cm.

Twenty Graafian follicles can be counted on the surface of the ovary and the largest is 0·2 cm. On section of the ovary the parenchymatous layer is found to contain innumerable small follicles.

No corpus luteum is present. A few remnants of previous corpora lutea are seen; these are light brown in colour and they measure 0·1 cm.

Right Ovary.—Weight, 1·10 gm.; measurements, 1·5 by 1·2 by 0·7 cm.

On section of the ovary fifteen Graafian follicles can be counted, the largest being 0·3 cm.

No corpus luteum is present, but a few remnants of previous corpora lutea are seen; the latter are light brown in colour and measure 0·1 cm.

(56) *Sheep No.* 25105.—Date slaughtered, 7th December, 1934; age, 6 years; condition, very good; weight, 95·0 lb.

Sexual History.

7.10.32 to 3.3.33 (148 days): anoestrous period.
4.3.33 to 7.8.33 (157 days): six exhibitions of oestrus.
8.8.33 to 11.1.34 (157 days): anoestrous period.
12.1.34 to 19.9.34 (251 days): thirteen exhibitions of oestrus.
20.9.34 to 7.12.34 (79 days): anoestrous period.

Uterus.—Weight, 30·5 gm.

Left Ovary.—Weight, 0·82 gm.; measurements, 1·5 by 1·2 by 0·8 cm.

Seventeen Graafian follicles can be counted on the surface of the ovary, but all are small, being 0·15 cm. in diameter. On section of the ovary the follicles are found congregated near the surface of the ovary and no large follicles are found.

No corpus luteum is present, but the remnants of five previous corpora lutea are seen.

Right Ovary.—Weight, 1·79 gm.; measurements, 1·9 by 1·4 by 1·2 cm.

The surface of the ovary is irregular, due to the presence of large and numerous Graafian follicles and a corpus luteum.

A total of nineteen follicles can be counted; there are two of 0·5 cm., one of 0·3 cm., several of 0·2 cm. in diameter, and the remainder are smaller.

The corpus luteum gives the ovary an abnormal shape and in addition the former has a projecting head of 0·15 cm. above the surface of the ovary. The head measures 0·3 cm. across, it has a slight depression in its centre, and it is skin-coloured. On section of the ovary through the corpus luteum, the latter is found to occupy two-thirds of the ovary. The corpus luteum measures 1·5 by 1·55 cm. and its substance is flesh coloured; it has a central cavity of 0·4 by 0·3 cm. the colour of which is slightly deeper flesh-coloured than the surrounding luteal tissue.

Two Graafian follicles measuring 0·4 and 0·5 cm. are found situated near the corpus luteum.

(57) *Sheep No.* 25908.—Date slaughtered, 14th December, 1934; age, 7 years; condition, good; weight, 83·5 lb.

Sexual History.

7.10.32 to 13.1.33 (99 days): anoestrous period.
14.1.33 to 1.9.33 (231 days): thirteen exhibitions of oestrus.
2.9.33 to 17.12.33 (107 days): anoestrous period.
18.12.33 to 2.9.34 (259 days): fourteen exhibitions of oestrus.
3.9.34 to 14.12.34 (103 days): anoestrous period.

Uterus.—Weight, 47·5 gm.

Left Ovary.—Weight, 1·37 gm.; measurements, 1·4 by 1·8 by 1·25 cm.

The ovary has an abnormal shape which is due to a large projecting corpus luteum on the free border of the ovary.

Four Graafian follicles, all 0·15 cm. and less, are seen. On section, a follicle of 0·4 cm. is found near the base of the corpus luteum.

A corpus luteum I is present. It projects 0·6 cm. above the surface of the ovary and it is pinkish in colour. The projecting portion measures 0·7 cm. across its head; it is almost circular and has overlapping margins; a slight irregular depression is present in the centre of the head. On section, the corpus luteum is found to be a solid body measuring, 1·2 by 0·8 cm., and its cut surfaces are pinkish in colour. The remnants of eight previous corpora lutea are seen.

Right Ovary.—Weight, 0·86 gm.; measurements, 1·45 by 1·2 by 0·9 cm.

Two Graafian follicles, measuring 0·4 and 0·2 cm., are seen on the surface of the ovary. On section of the ovary, six follicles can be counted. The largest follicle has been sectioned and it contains a clear fluid.

A small light yellow body, measuring 0·15 cm., is present in the ovary. This is very apparently a corpus luteum of the previous interovulation period and hence corpus luteum II. The remnants of twelve corpora lutea can be counted.

(58) *Sheep No.* 25938.—Date slaughtered, 14th September, 1934; age, 7 years; condition, good; weight, 72·0 lb.

Sexual History.

7.10.32 to 7.2.33 (124 days): anoestrous period.
8.2.33 to 11.6.33 (124 days): three exhibitions of oestrus.
12.6.33 to 10.4.34 (303 days): anoestrous period.
11.4.34 to 15.5.34 (35 days): two exhibitions of oestrus.
16.5.34 to 14.9.34 (122 days): anoestrous period.

Uterus.—Weight, 77·5 gm.

Left Ovary.—Weight, 1·52 gm.; measurements, 1·7 by 1·6 by 1·1 cm.

The surface of the ovary is irregular, due to projecting follicles, none of which exceed 0·2 cm., but the follicles have probably been pushed out by the existing corpus luteum.

A corpus luteum projects 0·1 cm. above the surface of the ovary; the projecting head has a slightly yellow colour and it has a slight indentation. When sectioned, the corpus luteum measures 1·0 by 0·7 cm., and consequently occupies a large space in the ovary. The cut surface is light yellow. This is a corpus luteum I. A few dark specks, representing the remnants of previous corpora lutea, are seen.

Right Ovary.—Weight, 1·22 gm.; measurements, 1·6 by 1·6 by 0·9 cm.

A large Graafian follicle, measuring 0·5 cm., gives the ovary an irregular shape; this follicle projects 0·2 cm. above the surface of the ovary. Several smaller follicles can be distinguished.

No corpus luteum is present, but some remnants of previous corpora lutea are seen.

(59) *Sheep No.* 35503.—Date slaughtered, 22nd November, 1934; age, 6 years; condition, very good; weight, 99·0 lb.

Sexual History.

7.10.32 to 27.2.33 (144 days): anoestrous period.
28.2.32 to 31.8.33 (185 days): ten exhibitions of oestrus.
1.9.33 to 29.12.33 (120 days): anoestrous period.
30.12.33 to 24.8.34 (238 days): eight exhibitions of oestrus.
25.8.34 to 22.11.34 (90 days): anoestrous period.

Uterus.—Weight, 47·5 gm.

Left Ovary.—Weight, 0·60 gm.; measurements, 1·3 by 1·0 by 0·8 cm.

Four Graafian follicles can be seen on the surface of the ovary, the largest being 0·2 cm.

A corpus luteum, projecting 0·05 cm. above the surface of the ovary, is present. On section, it is found to be almost oval in shape, the points of the oval pointing towards the poles of the ovary. The body measures 0·3 by 0·5 cm., the margins are almost white in colour, while the centre is a light yellow which is extended to the projecting portion. This is apparently a corpus luteum II. Eight remnants of previous corpora lutea occur as light and dark brown specks.

Right Ovary.—Weight, 2·63 gm.; measurements, 1·9 by 1·4 by 1·7 cm.

The abnormal shape of the ovary is due to the presence of large Graafian follicles and a newly formed corpus luteum.

Two very prominent Graafian follicles are seen, one is 0·7 cm. and the other 0·3 cm. in diameter.

The abnormal shape of the ovary is largely caused by the presence of a newly formed corpus luteum I, which occupies fully two-thirds of the ovary. The large prominence is red and several blood vessels can be seen transversing it. On section, the body is found to contain a slightly dull-coloured fluid, a portion of which is jelly-like and the latter becomes diffused with blood when irritated with a pin. The walls of the body, enclosing a large cavity of 1·1 by 0·9 cm., are thick, being 0·1 cm., and the surface of the cavity is pinkish. The remnants of nine previous corpora lutea are seen.

(60) *Sheep No.* 35504.—Date slaughtered, 9th November, 1934; age, 6 years; condition, very good; weight, 98·0 lb.

Sexual History.

7.10.32 to 14.2.33 (131 days): anoestrous period.
15.2.33 to 13.8.33 (180 days): eleven exhibitions of oestrus.
14.8.33 to 1.1.34 (141 days): anoestrous period.
2.1.34 to 15.9.34 (257 days): fifteen exhibitions of oestrus.
16.9.34 to 9.11.34 (55 days): anoestrous period.

Uterus.—Weight, 49·5 gm.

Left Ovary.—Weight, 1·14 gm.; measurements, 1·6 by 1·2 by 0·9 cm.

Fifteen small Graafian follicles, the largest of which is 0·2 cm., can be counted.

A corpus luteum appears on the surface of the ovary. It projects 0·05 cm. above the surface of the ovary and measures 0·175 cm. across the top or head. On section, the corpus luteum is found to extend 0·8 cm. into the ovary and to be 0·5 cm. in width. It is almost cone-shaped and has a large central depression, measuring 0·3 by 0·5 cm., which contains a fluid. The substance of the body is flesh-coloured but the colour of the depression is deep pink.

Right Ovary.—Weight, 0·91 gm.; measurements, 1·4 by 1·3 by 0·9 cm.

Six Graafian follicles can be counted in the ovary; the largest is 0·6 in diameter and it causes the ovary to bulge somewhat.

No corpus luteum is present, but the remnants of four previous corpora lutea are seen.

Group VIII.

Observations commenced 1st May, 1933.

Treatment.—On grazing: Green oat grazing during winter months; lick, *ad lib* (2 parts bone meal, 1 part salt).

(61) *Sheep No.* 21500.—Date slaughtered, 9th November, 1934; age, 6 years; condition, very good; weight, 84·0 lb.

Sexual History.

1.5.33 to 15.9.33 (138 days): eight exhibitions of oestrus.
16.9.33 to 31.12.33 (107 days): anoestrous period.
1.1.34 to 2.10.34 (275 days): seventeen exhibitions of oestrus.
3.10.34 to 9.11.34 (38 days): anoestrous period.

Uterus.—Weight, 45·5 gm.

Left Ovary.—Weight, 0·87 gm.; measurements, 1·6 by 1·1 by 0·8 cm.

Twelve Graafian follicles can be counted in the ovary; all the follicles are small and do not exceed 0·2 cm.

No corpus luteum is present, but nine remnants of previous corpora lutea can be seen.

Right Ovary.—Weight, 1·53 gm.; measurements, 1·4 by 1·2 by 1·4 cm.

The abnormal shape of the ovary is due to the presence of large Graafian follicles and a corpus luteum.

Two large Graafian follicles, measuring 0·8 and 0·5 cm. in diameter, are seen, and in addition several smaller follicles are present. The largest follicle has been cut into; it contains a clear fluid, its outer wall is thin, and its internal surfaces are reddish in colour.

A corpus luteum is present. It projects 0·6 cm. above the surface of the ovary and measures 0·5 cm. across its head. The external portion is pinkish in colour. On section, the substance of the body is dark flesh-coloured. It measures 1·2 by 1·0 cm. and there is a central depression. The remnants of three previous corpora lutea are seen.

(62) *Sheep No.* 22059.—Date slaughtered, 14th December, 1934; age, 6 years; condition, very good; weight, 87·0 lb.

Sexual History.

3.5.33 to 10.7.33 (69 days): five exhibitions of oestrus.
11.7.33 to 31.12.33 (174 days): anoestrous period.
1.1.34 to 4.9.34 (247 days): fourteen exhibitions of oestrus.
5.9.34 to 14.12.34 (101 days): anoestrous period.

Uterus.—Weight, 39·5 gm.

Left Ovary.—Weight, 0·72 gm.; measurements, 1·2 by 1·0 and 0·8 cm.

Eleven Graafian follicles can be counted in the ovary; the largest follicle is 0·4 cm.

No corpus luteum is present, but ten remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 1·13 gm.; measurements, 1·4 by 1·5 by 1·0 cm.

The ovary has an abnormal shape due to the presence of a corpus luteum.

Four small Graafian follicles, the largest of which is 0·15 cm., are present.

The corpus luteum causes the ovary to bulge. The bulge is a slight pink colour. On section, the corpus lueteum is found to occupy fully two-thirds of the ovary; the former measures 1·2 by 0·9 cm. and it is almost pear-shaped. The cut surface of the body is pink and there is no depression present. This is apparently a corpus luteum I.

(63) *Sheep No.* 25025.—Date slaughtered, 21st December, 1934; age, 6 years; condition, very good; weight, 97·0 lb.

Sexual History.

3.5.33 to 12.7.33 (71 days): five exhibitions of oestrus.
13.7.33 to 6.1.34 (178 days): anoestrous period.
7.1.34 to 11.7.34 (186 days): twelve exhibitions of oestrus.
12.7.34 to 21.12.34 (163 days): anoestrous period.

Uterus.—Weight, 47·5 gm.

Left Ovary.—Weight, 1·35 gm.; measurements, 1·7 by 1·5 by 1·0 cm.

Fourteen Graafian follicles can be counted in the ovary; the largest follicle is 0·4 cm. However, on section, a deeply seated follicle, measuring 0·6 cm., is exposed.

No corpus luteum is present and no remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 1·16 gm.; measurements, 1·7 by 1·6 by 0·9 cm.

The ovary is almost completely cone-shaped, the attached border of the ovary being the base of the cone. The abnormal shape of the ovary is due to the presence of a corpus luteum.

Ten Graafian follicles can be counted in the ovary; they are 0·1 cm. and less in diameter.

The corpus luteum projects 0·2 cm. above the surface of the ovary; the projection is very bright red in colour; it measures 0·4 cm. across its top and a small irregular depression is present. On section, the corpus luteum is found to measure 0·7 by 0·6 cm.; its cut surface is very bright pink and very soft. A small indefinitely outlined depression is present in the centre of the body. This is apparently a recently formed corpus luteum 1. The remnants of two previous corpora lutea are seen.

(64) *Sheep No.* 35708.—Date slaughtered, 22nd November, 1934; age, 7 years; condition, very good; weight, 83·0 lb.

Sexual History.

2.5.33 to 6.6.33 (36 days): three exhibitions of oestrus.
7.6.33 to 23.1.34 (231 days): anoestrous period.
24.1.34 to 5.8.34 (194 days): eleven exhibitions of oestrus.
6.8.34 to 22.11.34 (109 days): anoestrous period.

Uterus.—Weight, 40·0 gm.

Left Ovary.—Weight, 0·97 gm.; measurements, 1·6 by 1·2 by 0·8 cm.

Nine Graafian follicles are counted, the largest of which is 0·3 cm. in diameter.

No corpus luteum is present, but four remnants of previous corpora lutea are seen, and they are found to be irregular light brown specks, measuring 0·05 to 0·1 cm.

Right Ovary.—Weight, 1·05 gm.; measurements, 1·5 by 1·2 by 0·9 cm.

Fifteen Graafian follicles can be counted in the ovary; the largest follicles are 0·5 and 0·3 cm, but the majority are 0·1 and 0·2 cm. in diameter. The largest follicle bulges slightly above the surface of the ovary. This follicle has been cut through and it is found to contain a clear fluid.

No corpus luteum is present, but a few remnants of previous corpora lutea are seen.

(65) *Sheep No.* 35732.—Date slaughtered, 16th November, 1934; age, 6 years; condition, good; weight, 74·0 lb.

Sexual History.

2.5.33 to 10.7.33 (70 days): five exibitions of oestrus.
11.7.33 to 20.2.34 (225 days): anoestrous period.
21.2.34 to 24.7.34 (154 days): ten exhibitions of oestrus.
25.7.34 to 16.11.34 (115 days): anoestrous period.

Uterus.—Weight, 30·5 gm.

Left Ovary.—Weight, 0·60 gm.; measurements, 1·4 by 1·0 by 0·8 cm.

Eleven Graafian follicles can be counted in the ovary; the largest follicle is 0·3 cm.

No corpus luteum is present, but five remnants of previous corpora lutea are seen, occurring as dark brown specks.

Right Ovary.—Weight, 0·71 gm.; measurements, 1·3 by 1·2 by 0·8 cm.

Eight Graafian follicles can be counted in the ovary, the largest follicle being 0·3 cm. in diameter. The latter has been cut through and it contains a clear fluid.

No corpus luteum is present. Six remnants of previous corpora lutea are seen and above one of these is a small projection above the surface of the ovary. On section, the remnant is found to extend only 0·075 cm. into the substance of the ovary.

(66) *Sheep No.* 35994.—Date slaughtered, 7th December, 1934; age, 6 years; condition, very good; weight, 100·0 lb.

Sexual History.

3.5.33 to 10.8.33 (100 days): seven exhibitions of oestrus.
11.8.33 to 12.2.34 (186 days): anoestrous period.
13.2.34 to 18.9.34 (218 days): twelve exhibitions of oestrus.
19.9.34 to 7.12.34 (80 days): anoestrous period.

Uterus.—Weight, 37·0 gm.

Left Ovary.—Weight, 0·84 gm.; measurements, 1·4 by 1·3 by 0·8 cm.

Seven Graafian follicles can be counted on the surface of the ovary, but on section, a total of twelve follicles is apparent. The largest follicle measures 0·3 cm. in diameter.

No corpus luteum is present, but six remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 0·89 gm.; measurements, 1·5 by 1·2 by 0·9 cm.

One Graafian follicle, measuring 0·6 cm. in diameter, is very conspicuous; it projects 0·15 cm. above the surface of the ovary, and delicate blood vessels can be seen transversing its thin outer wall. A total of nine follicles can be counted in the ovary.

No corpus luteum is present, but four remnants of previous corpora lutea are seen.

(67) *Sheep No.* 37058.—Date slaughtered, 4th January, 1935; age, 7 years; condition, good; weight, 83·0 lb.

Sexual History.

2.5.33 to 3.9.33 (125 days): eight exhibitions of oestrus.
4.9.33 to 3.1.34 (122 days): anoestrous period.
4.1.34 to 9.9.34 (249 days): fifteen exhibitions of oestrus.
10.9.34 to 4.1.35 (117 days): anoestrous period.

Uterus.—Weight, 56·5 gm.

Left Ovary.—Weight, 0·75 gm.; measurements, 1·5 by 1·05 by 0·8 cm.

Five Graafian follicles are seen, the largest of which is 0·15 cm.

A blood-red spot occurs on the surface of the ovary. The section of the ovary has been made through this spot, which is found to contain a somewhat thick and slightly yellow fluid in a small cavity. The sectioned area is marked by the presence of a diffusion of blood and numerous small blood vessels can be seen.

A very dark black spot, measuring 0·1 cm., is seen near the above object. The former object when pricked is found to contain blood. This is a case of follicular haemorrhage.

No corpus luteum and no remnants of previous corpora lutea are present.

Right Ovary.—Weight, 0·74 gm.; measurements, 1·5 by 1·1 by 0·8 cm.

Four Graafian follicles can be counted in the ovary, the largest of which is 0·4 cm. The largest follicle has been cut through and it contains a clear fluid.

Two dark black spots are seen on the surface of the ovary. On section of the ovary, they are found to resemble the black spot found in the left ovary; the largest spot measures 0·2 cm.

A corpus luteum is present; it measures 0·5 by 0·3 cm. When sectioned its shape is irregular and its margins are indefinite. The cut surface of the body is light yellow in colour. It is apparently a corpus luteum I. The remnants of three previous corpora lutea are present.

(68) *Sheep No.* 37059.—Date slaughtered, 9th November, 1934; age, 6 years; condition, very good; weight 89·0 lb.

Sexual History.

1.5.33 to 27.8.33 (119 days): eight exhibitions of oestrus.
28.8.33 to 24.12.33 (119 days): anoestrous period.
25.12.33 to 30.9.34 (280 days): eleven exhibitions of oestrus.
1.10.34 to 9.11.34 (40 days): anoestrous period.

Uterus.—Weight, 51·5 gm.

Left Ovary.—Weight, 0·99 gm.; measurements, 1·5 by 1·4 by 1·0 cm.

A large projecting Graafian follicle gives the ovary an abnormal shape. This follicle is 0·7 cm. in diameter and it projects 0·4 cm. above the surface of the ovary. In addition, three follicles, 0·1 cm., are present. The large follicle has been cut into; it contains a clear fluid and its inner wall is pinkish in colour.

A corpus luteum is present. It projects 0·5 cm. above the surface of the ovary, and its exposed head is 0·1 cm. in diameter. On section of the body, it is found to be almost circular in shape with a diameter of 0·5 cm. A central depression is present; the cut surface is skin-coloured while the cavity is reddish. Six remnants of previous corpora lutea are present in the ovary.

Right Ovary.—Weight, 0·61 gm.; measurements, 1·4 by 1·0 by 0·8 cm.

Six small Graafian follicles, measuring 0·1 cm., are present in the ovary.

No corpus luteum is present, but seven remnants of previous corpora lutea are seen.

(69) *Sheep No.* 37061.—Date slaughtered, 4th January, 1934; age, 6 years; condition, very good; weight, 102·0 lb.

Sexual History.

4.5.33 to 13.7.33 (71 days): four exhibitions of oestrus.
14.7.33 to 16.1.34 (187 days): anoestrous period.
17.1.34 to 18.9.34 (245 days): fifteen exhibitions of oestrus.
19.9.34 to 4.1.35 (108 days): anoestrous period.

Uterus.—Weight, 47·0 gm.

Left Ovary.—Weight, 1·41 gm.; measurements, 1·65 by 1·3 by 1·1 cm.

Ten Graafian follicles can be counted in the ovary; there are two follicles of 0·4 cm., one of 0·3 cm., and the remainder are 0·1 cm. and less in diameter. On section of the ovary, the largest follicle is found to be 0·5 cm.; it has a thin wall and tranversing blood vessels are seen.

A corpus luteum is present and it has caused the abnormal shape of the ovary. The corpus luteum forms only a very small prominence on the surface of the ovary. The prominence is pinkish-yellow, and surrounding it the area is more pink and small blood vessels can be seen. On section, the corpus luteum measures 1·0 by 0·9 cm.; the cut surface is pale pink and a small irregular depression, measuring 0·2 cm., is present. This is a corpus luteum I. Two remnants of previous corpora lutea are present.

Right Ovary.—Weight, 0·63 gm.; measurements, 1·2 by 1·15 by 0·7 cm.

Nine Graafian follicles can be counted in the ovary, the largest is 0·2 cm.

No corpus luteum is present, but five remnants of previous corpora lutea are seen.

APPENDIX 3.

EXPERIMENT 4.

TABLES I AND II.—WEIGHTS OF SHEEP IN POUNDS.

TABLE I.

Group II.

Sheep No.	1933.						1934.								
	12.10.	27.10.	9.11.	25.11.	19.12.	23.12.	6.1.	20.1.	2.2.	17.2.	3.3.	17.3.	29.3.	14.4.	28.4.
25914	83·5	84·0	88·5	88·0	80·5	85·0	86·5	87·5	91·0	91·0	90·0	92·5	90·5	92·5	90·0
22031	79·5	86·5	90·0	87·0	83·0	87·5	89·0	88·0	90·0	87·0	83·5	89·0	86·5	91·0	93·0
22035	73·0	75·5	76·5	78·5	67·0	75·0	77·5	74·5	79·5	81·0	80·5	80·5	80·0	79·5	77·0
35610	72·0	72·5	79·0	75·5	71·0	74·0	76·0	75·0	81·0	77·5	79·0	79·5	75·0	79·0	76·5
35659	72·5	76·5	83·5	75·5	73·0	72·5	83·0	85·0	89·5	86·0	86·5	86·0	—	80·5	79·0
35701	70·5	73·0	75·0	71·5	65·0	68·0	74·0	71·5	77·5	72·0	77·5	77·0	77·0	72·0	77·5
35741	62·5	65·0	69·0	64·0	58·0	62·5	65·5	65·5	67·5	69·0	68·0	68·0	68·0	65·0	66·0
35755	76·5	84·0	85·5	73·0	81·0	85·0	86·0	83·0	89·0	89·5	91·5	92·5	89·5	90·5	91·0
35978	80·0	84·5	85·5	86·5	83·0	85·0	88·0	89·0	94·5	87·0	91·0	91·0	91·0	93·0	93·0
Totals	670·0	701·5	732·5	705·5	661·5	694·5	725·5	719·0	759·5	740·0	747·5	756·0	647·5	743·0	743·0
Averages	74·4	77·9	81·4	78·4	73·5	77·2	80·6	79·9	84·4	82·2	83·1	84·0	80·9	82·6	82·6

TABLE II.

Group III.

18449	—	—	82·5	78·5	74·0	75·5	78·5	76·5	87·5	80·5	82·0	87·0	84·0	86·0	87·5
35628	—	—	90·5	84·0	72·0	79·0	77·0	73·0	76·5	73·5	76·5	76·5	76·0	77·0	78·5
35656	—	—	74·5	68·0	62·0	61·5	66·5	63·0	65·5	67·0	66·0	65·5	65·0	66·5	66·0
35706	—	—	76·0	67·5	61·5	64·0	63·5	64·5	72·5	71·0	72·0	69·5	72·0	73·5	75·0
35712	—	—	71·0	68·0	63·5	64·5	68·5	67·5	71·5	70·5	68·5	73·0	71·5	73·5	71·0
35731	—	—	71·5	67·5	67·0	65·5	71·0	64·5	71·0	69·5	67·0	70·0	66·0	67·5	66·5
35734	—	—	72·0	69·5	60·0	68·0	63·0	62·0	65·5	62·5	63·0	63·0	62·5	63·5	64·5
38518	—	—	79·0	80·0	76·0	77·5	77·5	79·0	84·0	84·5	87·5	88·0	86·0	91·0	88·0
38521	—	—	76·0	73·5	67·0	66·5	68·0	68·0	68·5	70·0	68·0	69·5	70·0	70·0	69·0
Totals	—	—	633·0	666·5	603·0	612·0	633·5	618·0	662·5	649·0	650·5	662·0	653·0	668·5	666·0
Averages	—	—	77·0	74·0	67·0	68·0	70·0	68·7	73·6	72·1	72·3	73·6	72·6	74·3	74·0

THE SEXUAL ACTIVITY OF BREEDING EWES.

APPENDIX 3. EXPERIMENT 4.

TABLE III.

Group II.

Sheep No.	Date of lambing.	Occurrences of oestrus.											Remarks.
		1933.				1934.							
		Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	April.		May.	June.	
25914..	2.9.33	—	—	5.	14.	1, 19	5, 23	13, 30	, 17	Observations discontinued 30.4.34.	—	—	—
22031..	8.9.33	—	—	—	—	13.	1, 19	9.	14.		—	—	—
22035..	17.9.33	—	—	—	—	3, 19	6, 23	12, 30	. 17		—	—	—
35610..	22.9.33	—	—	—	—	—	, 18	. 25	12, 29		—	—	—
35659..	8.9.33	—	—	—	—	—	—	1, 19	4,		—	—	—
35701..	18.9.33	—	—	—	—	—	—	—	—		10,27	12,	Observations extended.
35741..	7.9.33	—	—	—	—	—	7, 25	—	4, 22		—	—	—
35755..	18.9.33	—	—	—	—	, 19	4, 21	10, 28	14,		—	—	—
35278..	29.9.33	—	—	—	10, 27	12,	15.	5, 21	8, 24		—	—	—

TABLE IV.

Group III.

Sheep No.	Date of lambing.	Occurrences of oestrus.										Remarks.
		1933.				1934.						
		Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	April.	May.	June.	
18449............	20.9.33	—	—	—	—	—	11,	1, 18	5, 22	—	—	—
35628............	9.9.33	—	—	—	—	—	. 16	. 28	—	—	—	—
35656............	2.9.33	—	—	—	—	—	—	—	—	—	—	Slaughtered, 15.8.34.
35706............	13.9.33	—	—	—	—	—	—	—	—	—	—	Slaughtered, 22.6.34.
35712............	29.9.33	—	—	—	—	—	—	13, 29	, 16	—	—	—
35731............	10.9.33	—	—	—	—	—	—	—	—	—	—	Slaughtered, 22.6.34.
35734............	2.9.33	—	—	—	—	—	. 22	11, 27	12, 28	—	—	—
38518............	20.9.33	—	—	—	—	5, 23	10, 28	, 18	6,	—	—	—
38521............	28.9.33	—	—	—	—	—	—	, 18	, 22	—	—	—

APPENDIX 3A.

EXPERIMENT 4.

THE EXAMINATION OF THE OVARIES OF INACTIVE SHEEP.

(1) *Sheep No.* 35656.—Date slaughtered, 15th August, 1934; age, 8 years; condition, poor; weight, 66·0 lb.; date of lambing, 1st September, 1933.

Sexual History.—No exhibition of oestrus was observed during the period 2nd September, 1933, to 15th August, 1934 or 347 days.

Left Ovary.—Weight, 0·89 gm.; measurements, 1·8 by 1·2 by 0·7 cm.

Several Graafian follicles are seen, two of which are prominent, with diameters of 0·5 cm., and the remainder small, measuring 0·1 to 0·2 cm. The two large follicles have been cut through and they contain a clear fluid.

No corpus luteum is present and no remnants of previous copora lutea are seen.

Right Ovary.—Weight, 0·48 gm.; measurements, 1·4 by 0·9 by 0·7 cm.

Numerous Graafian follicles are seen on the surface of the ovary, the three largest are 0·2 cm. in diameter.

No corpus luteum is present and no remnants of previous copora lutea are seen.

(2) *Sheep No.* 35706.—Date slaughtered, 22nd June, 1934; age, 6 years; condition, good; weight, 75·0 lb.

Sexual History.—No exhibition of oestrus was observed during the period 13th September, 1933, to 22nd June, 1934, or 352 days.

Left Ovary.—Weight, 0·55 gm.; measurements, 1·5 by 1·0 by 0·7 cm.

One prominent Graafian follicle measuring 0·4 cm. in diameter is present; the follicle projects 0·2 cm. above the surface of the ovary. A second follicle of 0·2 cm. is seen in close proximity to the large follicle.

No corpus luteum is present. The remnants of several previous corpora lutea are seen occurring as dark specks.

Right Ovary.—Weight, 0·97 gm.; measurements, 1·7 by 1·0 by 0·9 cm.

Only one small Graafian follicle of 0·1 cm. is seen.

A cone shaped corpus luteum, red in colour and measuring 1·0 by 0·9 cm. is present. It is a corpus luteum (1). Several remnants of previous corpora lutea are seen.

(3) *Sheep No.* 35731.—Date slaughtered, 22nd June, 1934; age, 6 years; condition, fair; weight, 66·5 lb.

Sexual History.—No exhibition of oestrus was observed during the period 10th September, 1933, to 22nd June, 1934, or 355 days.

Left Ovary.—Weight, 0·56 gm.; measurements, 1·5 by 1·0 by 0·7 cm.

Two Graafian follicles are seen, the larger is 0·3 cm. in diameter.

No corpus luteum is present, but the remnants of several previous corpora lutea are seen.

Right Ovary.—Weight, 0·60 gm.; measurements, 1·2 by 1·2 by 0·7 cm.

Two Graafian follicles are seen, the larger of which is 0·15 cm.

No corpus luteum is present, but several remnants of previous corpora lutea are seen occurring as dark specks.

APPENDIX 4.

EXPERIMENT 5.

TABLES I AND II.—WEIGHTS OF SHEEP IN POUNDS.

TABLE I.

Group I.

Sheep No.	1933.																1934.										
	25.5.	8.6.	23.6.	6.7.	21.7.	4.8.	18.8.	31.8.	15.9.	28.9.	12.10.	27.10.	9.11.	25.11.	9.12.	23.12.	6.1.	20.1.	2.2.	17.2.	3.3.	17.3.	29.3.	14.4.	28.4.	12.5.	29.5.
29860	108·0	105·5	100·5	94·0	86·5	85·5	81·5	80·0	83·5	86·0	90·5	90·5	99·0	93·5	102·0	106·0	111·5	111·5	116·0	113·5	115·0	117·5	118·0	118·0	117·0	115·5	105·5
29946....	107·5	106·5	102·0	98·0	90·5	89·0	84·5	81·5	84·5	87·0	93·5	98·5	101·0	101·0	107·0	108·0	111·5	111·0	115·0	116·5	118·0	118·0	115·0	119·5	114·0	117·0	110·5
29958....	114·0	110·0	104·5	98·5	92·5	92·5	89·0	88·5	89·0	88·5	93·0	99·0	100·0	107·0	108·5	109·5	117·0	116·0	121·0	119·5	120·5	124·0	124·5	126·0	123·5	124·0	125·0
30020....	104·0	104·0	95·5	90·0	83·5	80·0	74·5	77·5	79·0	80·5	86·5	86·0	91·0	94·0	101·5	103·0	110·5	110·0	118·0	118·5	117·0	119·5	120·0	121·5	123·0	122·5	116·0
30033....	103·5	100·5	96·0	88·5	86·5	84·5	78·0	81·5	76·0	81·0	90·0	91·0	100·5	99·5	107·0	103·5	110·5	112·0	118·0	110·0	121·0	116·0	117·5	121·0	121·0	112·0	113·0
30067....	112·5	109·0	103·0	96·0	101·5	98·0	94·5	88·5	90·0	96·0	95·5	103·0	107·5	108·5	112·0	115·0	122·0	120·0	125·0	123·0	121·0	129·0	128·0	129·5	130·0	131·0	130·5
32367....	113·5	111·5	105·0	101·5	94·5	90·5	84·5	86·5	85·5	90·0	96·0	96·5	100·5	104·0	108·0	115·0	118·5	115·5	121·5	122·0	126·5	126·5	126·0	129·0	126·0	122·0	121·0
32390....	102·0	97·0	91·5	89·5	82·0	76·5	71·5	71·5	74·5	78·5	85·5	90·0	91·5	91·0	99·0	102·5	109·0	108·5	115·5	113·5	116·0	117·5	117·5	118·5	120·0	117·5	115·0
38079....	92·5	90·5	85·5	80·5	74·5	70·5	66·5	66·5	64·5	65·5	72·0	72·5	77·5	74·0	75·5	82·5	86·5	85·5	86·5	86·0	86·5	88·5	88·0	90·0	89·0	85·5	80·0
38080....	117·0	112·5	112·5	104·5	105·5	101·0	93·5	93·5	93·0	95·0	102·5	107·5	112·0	114·5	120·0	125·0	129·5	130·0	136·5	134·5	—	131·0	128·0	133·0	126·0	128·0	120·5
Totals....	1074·5	1047·0	996·0	941·0	897·5	868·0	818·0	815·5	819·5	848·0	905·0	934·0	980·5	987·5	1040·5	1070·0	1126·5	1120·0	1173·0	1157·0	1041·5	1189·5	1172·5	1216·0	1189·5	1175·0	1137·0
Averages.	107·4	104·7	99·6	94·1	89·8	86·8	81·8	81·6	82·0	84·8	90·5	93·4	98·0	98·8	104·0	107·0	112·6	112·0	117·3	115·7	115·7	119·0	117·2	121·6	119·0	117·5	113·7

TABLE II.

Group II.

35155....	61·5	59·0	57·0	56·5	54·0	49·0	49·5	51·5	52·5	56·0	57·5	58·5	63·5	62·5	62·5	69·0	74·5	69·5	76·0	75·0	80·0	81·0	79·5	82·5	82·0	81·0	80·5
35158....	59·0	56·5	55·5	55·0	52·5	51·5	51·0	50·5	52·5	57·0	59·5	61·0	65·0	60·5	63·0	66·0	69·0	66·5	75·0	72·5	70·0	72·5	73·5	73·0	76·5	73·0	74·0
35159....	56·5	53·5	52·0	51·5	50·0	47·5	46·0	44·5	48·5	52·0	53·5	56·0	58·5	59·5	55·0	59·0	60·5	62·0	62·0	66·5	65·5	67·0	68·0	73·0	67·5	68·5	68·5
35197....	62·0	62·5	60·5	61·5	58·5	57·0	52·0	52·5	51·5	55·0	57·0	60·0	65·0	64·5	65·5	68·5	72·0	70·5	72·0	75·5	76·5	77·5	76·0	75·5	76·5	79·5	77·5
35210....	48·0	48·0	47·0	47·0	45·0	43·0	43·5	44·0	45·0	49·0	51·5	53·5	59·5	57·5	58·5	63·5	64·0	62·5	67·0	68·5	70·0	70·0	70·0	71·5	69·5	71·0	69·5
35216....	51·0	50·5	48·0	47·0	43·0	43·0	40·5	41·5	42·5	49·5	50·5	55·5	58·0	62·0	60·0	66·0	69·0	70·5	71·5	72·5	76·0	74·0	72·0	75·0	76·0	77·0	74·5
35217....	62·5	61·0	57·0	56·5	51·5	50·0	48·0	50·5	50·0	54·0	58·0	59·5	62·0	62·5	65·5	67·0	70·5	68·5	74·5	71·0	75·5	76·5	75·0	79·0	81·0	78·5	77·5
35219....	60·0	58·0	56·5	56·0	54·5	54·0	53·0	53·5	56·5	60·0	63·5	64·5	69·0	71·0	66·0	72·5	74·5	72·0	75·0	76·5	77·0	78·5	76·0	77·0	80·0	78·5	77·0
35223....	54·5	52·5	50·0	49·0	46·0	43·5	43·0	43·5	46·5	50·0	53·5	55·5	62·0	60·0	65·0	70·5	74·0	68·5	78·5	80·0	79·0	82·5	82·0	85·0	83·0	80·5	81·0
35238....	46·5	44·5	43·0	42·0	40·5	37·5	37·0	38·5	39·5	45·0	47·5	48·5	53·5	52·0	54·0	57·0	60·0	58·0	59·5	60·5	62·0	63·0	61·0	65·0	64·0	63·0	61·0
Totals....	561·5	546·0	526·5	522·0	495·5	476·0	463·5	470·5	495·0	527·5	552·0	572·5	616·0	612·0	615·0	659·0	688·0	662·5	711·0	718·5	731·5	742·5	733·0	756·5	756·0	750·5	741·0
Averages.	56·2	54·6	52·6	52·2	49·6	47·6	46·4	47·0	48·5	52·8	55·2	57·2	61·6	61·2	61·5	65·9	68·8	66·8	71·1	71·8	73·2	74·2	73·3	75·6	75·6	75·0	74·1

OESTROUS OBSERVATIONS AND THE SEXUAL SEASONS OF CROSSBRED SHEEP.

APPENDIX 4. **EXPERIMENT 5.**

TABLE III.

Group I.

Sheep No.		1933.								1934.					Sexual season (1933), May to August.	No. of dioestrous cycles.	Anoestrous period (1933-34). September to January. (Days.)	Sexual season (1934), February to May.	No. of dioestrous cycles.
		May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	April.	29th May.	Periodicity of oestrus in days.			Periodicity of oestrus in days.	
39860....	Oestrous observations commenced on 24.5.33.	, 25	11, 27	12, 31	—	—	—	—	—	—	, 21	10, 25	10, 26	12, 28	17 16 15 19	5	205	17 15 16 16 16 16	7
29946....		—	5, 20	, 23	—	—	—	—	—	—	—	11, 27	12, 27	12, 28	15 33	3	231	16 16 15 15 16	6
29958....		, 24	10, 27	14, 31	, 18	—	—	—	—	—	—	—	3, 20	7, 24	17 17 17 17 18	6	228	17 17 17	4
30020....		, 24	10, 27	15,	—	—	—	—	—	—	, 22	10, 27	13, 30	, 16	17 17 18	4	222	16 17 17 17 16	6
30033....		, 29	15,	1, 18	—	—	—	—	—	—	—	8, 25	9, 25	12, 28	17 16 17	4	233	17 15 16 17 16	6
30067....		—	7, 23	10, 28	—	—	—	—	—	—	, 23	12, 30	, 18	5, 21	16 17 18	4	210	17 18 19 17 16	6
32367....		—	1, 17	3, 19	4,	—	—	—	—	—	—	7, 23	8, 24	10, 27	16 16 16 16	5	215	16 16 16 16 17	6
32390....		—	7, 24	12,	—	—	—	—	—	—	—	15,	, 16	2, 18	17 18	3	246	32 16 16	4
38079....		, 25	9, 25	12, 29	—	—	—	—	—	—	—	, 17	1, 17	2, 18	15 16 17 17	5	231	15 16 15 16	5
38080....		, 24	8, 25	12.	—	—	—	—	—	—	—	10, 26	11, 27	13, 29	15 17 17	4	241	16 16 16 16 16	6

TABLE IV.

Group II.

Sheep No.		May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	April.	29th May.	Periodicity of oestrus in days.	No. of dioestrous cycles.	Anoestrous period (Days.)	Periodicity of oestrus in days.	No. of dioestrous cycles.
35155....	Oestrous observations commenced on 24.5.33.	—	—	—	—	—	—	—	—	—	—	4,	, 25	—		0	284+	52	2
35158....		, 31	—	—	—	—	—	—	—	7, 26	11, 28	, 17	3, 21	8,		1	221	19 16 17 17 17 18 17	8
35159....		—	—	—	—	—	—	—	—	1,	—	, 16	—	9, 28		0	222+	74 54 19	4
35197....		, 28	15,	2, 19	—	—	—	—	—	—	2, 19	9, 27	13, 30	, 17	18 17 17	4	198	17 18 18 17 17 17	7
35210....		—	—	—	—	—	—	—	—	—	20, 27	, 16	3, 20	8, 26,		0	262+	17 17 18 17 18 18	7
35216....		, 25	—	—	—	—		—	6,	13, 30	, 17	7, 24	12, 29	17,		1	195	38 17 18 18 17 19 17 18	9
35217....		, 25	—	—	—	—	—	—	—	1, 18	5, 24	12, 29	—	3, 21		1	221	17 18 19 16 17 35 18	8
35219....		—	—	—	—	—	—	—	—	—	1, 18	8, 26	13, 30	19,		0	253	17 18 18 18 17 19	7
35223....		—	—	—	—	—	—	—	—	, 22	8, 25	14,	, 18	4,		0	230+	17 17 17 35 16	6
35238....		—	—	—	—	—	—	—	—	—	—	9, 27	, 16	3, 21		0	289+	18 20 17 18	5

TABLE V.*

Group III.

Sheep No.		May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	April.	29th May.	Periodicity of oestrus in days.	No. of dioestrous cycles.	Anoestrous period (Days.)	Periodicity of oestrus in days.	No. of dioestrous cycles.
15257....	Oestrous observations commenced on 24.5.33.	—	3, 20	8, 27	—	1,	—	—	, 29	, 15	, 19	9, 26	12,	15.	17 18 19 36	5	118	17 35 18 17 17 33	7
15327....		—	3,	7, 25	10,	—	—	—	—	—	4, 20	9.	—	—	34 18 16	4	177	16 17	3
21504....		—	6,	—	—	—	—	—	—	—	—	—	—	14,	— — —	1	341	— —	1
21607....		, 27	13, 30	, 17	3	Died 30.9.33.									17 17 17 17	5	—	— —	—
24928....		, 26	13,	1, 19	5,	—	—	—	—	—	8, 26	, 16	2, 19	, 24	18 18 18 17	5	186	18 18 17 17 35	6
25873....		, 31	, 18	6, 24	12	—	—	—	—	—	, 17	6, 24	11, 29	, 17	18 18 18 19	5	188	17 18 18 18 18	6
35501....		, 27	—	—	—	—	—	—	—	—	—	7, 27	13, 30	, 18	— — — —	1	283	20 17 17 18	5
35496....		, 24	11, 28	, 16	—	—	—	—	—	—	, 18	8, 26	12, 29	, 17	18 17 18	4	216	18 18 17 17 18	6
35502....		—	8, 26	14,	1,	—	—	—	—	—	, 23	12, 30	, 17	4, 22	18 18 18	4	205	17 18 18 17 18	6
35497....		—	1, 19	8,	12, 29	—	—	—	—	3, 19	6,	13, 30	—	4, 21	18 19 35 17	5	126	16 18 35 35 17	7

* NOTE.—The records of Group III have been extracted from Experiment 1, Appendix 1, Table XIV.

APPENDIX 5.

EXPERIMENT 6.

TABLES 1–IV.—WEIGHTS OF SHEEP IN POUNDS.

TABLE I.

Group I.—(Border Leicester-Merino Crossbreds, 1933).

Sheep No.	Date of birth.	Weight at birth.	Weights at:							
			3 months.	6 months.	9 months.	12 months.	15 months.	18 months.	21 months.	24 months.
38320......	21.9.33	8·5	31·0	50·0	45·0	47·0	52·5	54·0	62·5	61·5
38321......	8.9.33	9·0	39·5	55·5	53·5	52·0	67·0	67·0	83·0	90·0
38342......	30.8.33	8·0	46·5	62·0	50·5	57·0	64·5	72·5	79·5	90·5
38374......	11.9.33	8·5	45·5	62·0	50·0	63·0	71·5	76·5	81·5	82·0
38385......	14.9.33	9·0	44·5	61·0	55·0	67·0	78·5	82·0	84·0	86·5
38399......	17.9.33	8·0	39·0	52·0	40·0	48·0	64·5	65·0	73·0	77·0
38400......	11.9.33	7·5	34·0	49·0	37·0	45·5	57·5	58·5	61·5	63·0
38427......	23.9.33	11·0	43·5	63·5	56·5	69·5	81·0	80·0	87·0	91·5
38430......	24.9.33	9·0	38·5	55·0	49·5	56·5	66·5	67·0	—	—
38436......	24.9.33	9·5	40·5	61·5	60·0	59·0	66·5	76·0	—	—
Totals............		88·0	402·5	571·5	497·0	564·5	650·0	699·0	612·0	642·0
Averages.........		8·8	40·2	57·2	49·7	56·4	65·0	69·9	76·5	80·2

TABLE II.

Group II.—(Merinos, 1933).

Sheep No.	Date of birth.	Weight at birth.	3 months.	6 months.	9 months.	12 months.	15 months.	18 months.	21 months.	24 months.
38347......	2. 9.33	8·0	32·5	40·5	35·0	58·5	64·0	68·0	75·0	77·5
38349......	3. 9.33	8·5	31·5	38·5	32·0	51·0	47·0	45·5	46·0	44·0
38351......	1. 9.33	8·5	39·0	46·0	39·0	55·0	55·5	57·5	55·5	51·0
38361......	10. 9.33	8·5	41·5	54·5	46·0	60·0	66·0	66·0	76·0	74·5
38404......	13. 9.33	8·0	35·5	42·0	35·0	38·5	52·5	55·0	52·5	53·5
38406......	11. 9.33	8·5	28·5	41·0	35·5	53·0	54·5	52·0	51·5	53·0
38450......	25. 9.33	9·0	37·5	53·0	47·0	52·0	58·5	61·0	67·5	66·0
38469......	1.10.33	7·0	24·5	41·5	36·0	43·0	51·0	55·5	53·0	62·0
38479......	5.10.33	8·0	32·0	54·5	49·5	60·5	62·0	62·5	64·0	65·0
38536......	17.10.33	9·0	28·0	42·0	37·0	49·0	55·0	53·0	54·5	54·5
Totals............		83·0	330·5	453·5	392·0	520·5	566·0	576·0	595·5	601·0
Averages.........		8·3	33·0	45·4	39·2	52·0	56·6	57·6	59·6	60·1

TABLE III.

APPENDIX 5. EXPERIMENT 6.

Group III.—(Border Leicester-Merino Crossbreds, 1934).

Sheep No.	Date of births.	Weight at birth.	Weights at:			
			3 months.	6 months.	9 months.	12 months.
		lb.	lb.	lb.	lb.	lb.
41241............	9.9.34	10·0	51·0	58·5	55·0	44·5
41247............	11.9.34	7·5	38·5	44·0	45·5	44·0
41255............	12.9.34	9·0	40·5	54·0	50·0	47·5
41258............	13.9.34	7·0	35·0	54·0	54·0	53·5
41259............	5.9.34	9·5	50·0	64·0	70·0	68·0
41304............	20.9.34	10·0	40·5	55·0	55·5	57·0
41316............	7.9.34	9·5	39·0	54·0	50·5	49·5
41329............	9.9.34	10·0	40·0	51·0	49·0	52·5
41337............	28.9.34	9·5	42·0	60·5	64·0	61·5
41362............	8.9.34	9·0	27·5	45·5	45·5	48·5
Totals.................		91·0	404·0	542·5	539·0	527·0
Averages..............		9·1	40·4	54·2	53·9	52·7

TABLE IV.

Group IV.—(Merinos, 1934).

41275............	16.9.34	9·5	35·5	39·5	37·0	34·0
41276............	17.9.34	8·5	32·5	35·5	41·5	46·0
41295............	19.9.34	10·5	32·0	37·0	35·5	37·0
41311............	22.9.34	7·5	36·0	37·5	41·0	33·0
41383............	6.10.34	10·5	36·0	48·0	49·0	50·5
41349............	1.10,34	9·0	34·0	44·5	45·0	41·0
41394............	10.10.34	10·0	28·5	41·0	47·5	50·0
41605............	11.10.34	8·5	33·5	41·5	44·5	45·5
41614............	12.10.34	9·5	34·0	46·0	57·5	62·5
41616............	12.10.34	9·0	36·5	41·5	50·5	54·0
Totals.................		92·5	338·5	412·0	449·0	435·5
Averages..............		9·2	33·8	41·2	44·9	45·4

APPENDIX 6.

EXPERIMENT 7.

TABLES I–VIII.—WEIGHTS OF SHEEP IN POUNDS.

Group I.

Sheep No.	1935.																	
	23.3.	30.3.	13.4.	27.4.	11.5.	25.5.	8.6.	22.6.	6.7.	20.7.	3.8.	17.8.	31.8.	14.9.	28.9.	12.10.	26.10.	9.11.
41629	41·0	43·0	44·5	44·5	38·0	41·5	44·0	44·0	45·5	44·0	46·0	44·0	44·0	44·5	47·0	40·5	38·0	42·5
41641	49·5	51·5	50·5	50·0	47·5	52·5	54·0	50·5	55·0	53·5	55·0	56·0	54·5	53·5	57·5	48·5	46·0	51·0
41647	35·0	38·0	37·0	38·0	35·5	37·0	36·0	36·5	39·0	38·0	42·5	35·5	34·0	36·0	38·0	32·0	31·0	37·0
41648	44·5	46·5	45·5	47·0	44·5	45·5	44·0	44·0	45·5	44·0	46·0	46·0	40·0	42·5	45·5	39·0	38·5	43·0
42393	41·5	43·0	42·5	42·0	40·5	42·5	43·5	42·0	42·0	43·5	44·5	43·0	42·5	45·0	46·5	38·0	39·0	43·0
42394	43·0	45·5	46·0	45·5	45·0	46·0	45·5	48·0	48·0	47·5	54·5	46·5	53·0	51·5	52·0	46·0	44·0	48·0
42396	39·0	42·0	43·0	44·5	42·0	45·0	44·5	45·0	46·0	45·5	48·0	46·0	44·0	44·5	47·0	39·5	40·5	43·0
42397	44·5	47·5	47·0	47·5	44·0	48·5	49·5	49·0	50·0	49·0	51·5	47·5	49·0	47·5	50·0	43·0	41·0	45·5
42398	43·0	45·5	44·0	46·0	42·0	45·5	45·5	45·0	45·5	43·0	47·0	42·0	43·0	41·0	43·5	36·0	37·0	42·0
42399	39·0	40·0	40·5	41·5	38·5	40·5	42·5	43·0	44·0	42·5	45·0	42·0	41·5	39·0	41·0	33·5	31·5	37·0
Totals	420·0	442·5	440·5	446·0	417·5	444·5	449·0	447·0	460·5	450·5	480·0	448·5	445·5	445·0	468·0	396·0	386·5	432·0
Averages	42·0	44·2	44·0	44·6	41·8	44·4	44·9	44·7	46·0	45·0	48·0	44·8	44·5	44·5	46·8	39·6	38·6	43·2

TABLE II. *Group II.*

Sheep No.	23.3.	30.3.	13.4.	27.4.	11.5.	25.5.	8.6.	22.6.	6.7.	20.7.	3.8.	17.8.	31.8.	14.9.	28.9.	12.10.	26.10.	9.11.
41624	39·0	40·0	43·5	44·5	47·5	50·5	52·5	52·0	56·5	58·0	60·5	63·0	66·5	69·5	70·5	64·0	65·5	70·0
41625	41·0	42·5	44·0	45·5	47·0	49·0	51·0	52·0	57·0	57·5	61·0	64·0	65·5	67·5	70·5	64·0	67·0	68·0
41630	36·5	39·5	42·5	46·5	49·0	50·0	51·5	53·0	56·0	57·0	60·0	61·5	65·5	65·0	65·0	57·5	58·5	63·5
41632	44·5	43·5	47·0	48·0	51·0	52·0	52·0	51·5	55·5	56·0	57·0	57·5	60·5	63·0	65·0	58·5	69·5	64·0
41639	42·0	43·0	45·0	49·5	52·0	50·5	52·0	52·5	57·5	59·0	62·0	62·0	68·0	69·0	69·5	60·5	63·0	66·0
41640	43·0	46·0	50·5	51·5	54·0	55·5	58·5	57·5	61·0	60·0	64·5	65·0	69·5	68·5	68·5	58·5	60·5	66·5
41642	41·5	44·0	43·5	46·5	49·0	50·0	50·0	50·0	54·5	57·0	60·0	61·5	66·5	68·0	71·5	66·0	68·0	70·0
41650	46·0	46·5	48·5	52·0	54·0	55·5	58·0	58·0	65·0	68·0	70·0	70·5	75·0	78·0	79·5	69·0	72·0	76·5
41652	42·5	42·0	43·0	47·0	46·5	48·0	51·0	51·0	57·0	58·5	61·5	62·5	68·0	70·0	65·5	63·5	65·0	67·5
42395	39·0	42·0	41·5	44·0	46·0	46·0	49·0	47·5	53·0	54·0	58·0	57·0	62·5	63·0	64·0	52·0	55·0	60·0
Totals	415·0	429·0	448·5	474·0	496·0	507·0	525·5	525·0	573·0	585·0	614·5	624·5	667·5	681·5	689·5	613·5	644·0	672·0
Averages	41·5	42·9	44·8	47·4	49·6	50·7	52·5	52·5	57·3	58·5	61·4	62·4	66·7	68·2	69·0	61·4	64·4	67·2

WEIGHTS OF SHEEP IN POUNDS—(*continued*).

TABLE III. *Group III.*

Sheep No.	1935.																	
	23.3.	30.3.	13.4.	27.4.	11.5.	25.5.	8.6.	22.6.	6.7.	20.7.	3.8.	17.8.	31.8.	14.9.	28.9.	12.10.	26.10.	9.11
41623............	41·0	40·5	45·0	47·0	50·5	51·0	53·0	52·5	58·5	60·0	63·0	62·0	66·5	69·5	70·5	62·5	68·0	70·0
41626............	41·5	43·5	44·5	47·5	49·0	49·5	51·5	53·0	54·0	57·5	61·5	63·5	67·0	69·5	69·0	58·0	62·0	67·0
41627............	43·5	45·0	48·5	50·5	53·0	53 0	56·0	55·0	59·0	59·0	61·0	65·5	67·5	69·0	71·5	63·0	63·5	67·5
41628............	39·5	40·5	41·5	44·5	46·5	47·0	49·0	49·0	51·0	51·0	54·5	56·0	58·5	60·5	59·5	52·5	56·5	59·0
41635............	45·0	47·0	48·5	51·5	55·0	55·5	57·0	57·0	62·0	62·0	64·5	66·0	69·0	70·0	72·5	61·5	65·5	69·5
41638............	37·0	39·0	41·5	45·5	47·5	50·0	52·5	52 5	56 0	57·0	57·5	59·0	62·0	62·5	65·0	58·0	60·0	60·0
41644............	45·5	43·5	45·5	47·5	51·0	51·5	54·0	53·5	56 5	57·0	59 5	60·5	64·5	66·0	65 0	59·5	62·0	64·5
41645............	42·5	40·5	44·0	46·0	50·0	49·5	51·0	51·5	56·0	57·5	58·0	62·0	64·5	65·0	66·0	60·0	60·0	62·5
41649............	44·0	45·5	48·5	50·0	53·0	52 5	56·5	55·0	59·5	61·0	64·5	63·5	69·0	71 0	71·5	65·5	67·0	70·5
42392............	38·5	39·5	41·5	44 0	46·5	47·0	48·5	50·0	53·5	55·5	58 5	57 0	62·0	68·0	68·0	59·0	60·5	65·0
Totals........	418·0	424·5	449·0	474·0	502·0	503·5	529·0	529·0	566·0	577·5	602·5	615·0	650·5	671·0	678·5	599·5	625·0	655·5
Averages.....	41·8	42·4	44·9	47·4	50·2	50·4	52 9	52·9	56·6	57·8	60·2	61·5	65·0	67·1	67·8	60·0	62·5	65·6

TABLE IV. *Group IV.*

Sheep No.	23.3.	30.3.	13.4.	27.4.	11.5.	25.5.	8.6.	22.6.	6.7.	20.7.	3.8.	17.8.	31.8.	14.9.	28.9.	12.10.	26.10.	9.11
41633............	42·0	44·5	46·5	48·5	51·0	50·5	53·0	53·5	58·0	61·0	63·0	61·5	66·0	66·0	67·5	61·0	60·5	65·0
41634............	44·0	47·0	50·0	55·0	56·0	56·5	60·0	62·5	66·0	69·5	70·5	70·0	73·5	76·0	77·5	70·5	71·0	76·0
41636............	37·0	40·5	42·5	46·0	47·0	48·5	50·5	51·5	54 5	57·5	59·0	60·5	63·0	65·0	66·5	60·0	62·0	66·0
41637............	40·5	42·0	45·0	47·5	49·0	50·0	52·5	56·0	61·0	62·5	64·0	68 0	69·0	71·0	69·5	62·0	67·0	69·5
41631............	44·0	46·0	48·0	52·5	54·0	54·5	56·5	59·5	64·0	66·0	67·5	67·0	70·5	73·0	73·0	63·5	66·0	68·5
41643............	38 0	41·0	43·0	46·5	49·0	48·5	50·5	52·0	57·0	58·5	59·0	58·5	62·0	63·0	63·5	58·0	59·0	61·5
41646............	45·0	47·5	53·5	57·5	62·0	61·0	66 0	67 5	75·0	78·0	80·5	82·0	87·0	90·0	89·5	79·5	83·0	85·5
41651............	45·0	47·5	51·0	53·5	57·5	57·5	61 5	62·5	69·5	71 0	75·5	76 5	79·0	81·5	83·0	74·5	77·5	80·0
42390............	43·5	47·0	49·5	50·0	53·0	52·5	56 5	56·0	60·5	64·0	64·0	64·0	67·0	68·0	68·5	60·0	61·5	64·0
42391............	39·5	43·5	46·0	47·0	50·0	47·5	50·5	53·5	55·5	59·0	61 5	63·0	69·5	71·5	72·5	66·5	69·0	71·5
Totals........	418·5	446·0	475·0	504·0	528·5	527 0	557 5	574·5	621·0	657·0	664·5	671·0	709·5	725·0	733·0	655·5	666·5	707·5
Averages.....	41·9	44·6	47·5	50·4	52·8	52 7	55 8	57·5	62·1	65 7	66·4	67·1	70·9	72·5	73·3	65·6	66·6	70·8

WEIGHTS OF SHEEP IN POUNDS—(*continued*).

TABLE V.

APPENDIX 6. *Group V.* EXPERIMENT 7.

Sheep No.	23.7.35.	21.8.35.	18.9.35.	23.10.35.	7.11.35.
M. 1	58·0	60·0	58·0	60·5	51·0
M. 2	70·0	72·0	73·0	73·0	61·5
M. 3	69·0	71·5	70·5	78·0	69·5
M. 4	57·5	62·0	62·5	66·5	59·0
M. 5	61·0	65·5	62·5	65·5	54·5
M. 6	64·5	69·0	65·0	66·5	57·0
M. 7	71·5	74·0	74·0	79·5	74·0
M. 8	61·5	65·5	63·5	68·0	58·0
M. 9	63·5	65·5	65·5	70·0	61·5
M. 10	57·5	61·0	59·0	62·5	55·0
Totals	634·0	666·0	653·5	690·0	601·0
Averages	63·4	66·6	65·4	69·0	60·1

TABLE VI.

Group VI.

Sheep No.	25.3.35.	22.4.35.	20.5.35.	18.6.35.	16.7.35.	12.8.35.	9.9.35.	7.10.35.	4.11.35.
3	39·0	40·0	40·0	42·5	44·0	47·5	52·5	54·5	49·5
4	43·5	47·0	48·5	50·5	52·5	55·5	59·5	60·5	55·5
6	42·5	48·5	49·0	52·5	54·0	57·0	63·0	65·0	59·5
9	47·0	52·0	50·5	58·0	61·5	66·0	71·0	75·0	68·0
13	38·5	44·0	47·0	52·5	57·5	62·5	66·5	71·0	65·0
17	40·5	44·0	41·0	43·5	46·5	51·5	53·5	56·0	51·5
18	42·5	44·0	43·5	49·0	52·5	55·5	56·5	60·0	54·0
21	40·5	42·0	39·0	43·0	47·0	51·0	53·0	59·0	54·5
25	36·5	39·0	38·5	42·0	44·5	48·5	53·0	55·0	52·0
29	41·5	44·0	45·0	49·0	50·5	53·0	57·0	60·5	58·0
Totals	412·0	444·5	442·0	482·5	510·5	548·0	585·5	615·5	567·5
Averages	41·2	44·4	44·2	48·2	51·0	54·8	58·6	61·6	56·8

WEIGHTS OF SHEEP IN POUNDS—(*continued*).

TABLE VII.

APPENDIX 6. *Group VII* EXPERIMENT 7.

Sheep No.	25.3.35.	22.4.35.	20.5.35.	18.6.35.	16.7.35.	12.8.35.	9.9.35.	7.10.35.	4.11.35.
7	36·5	38·5	37·5	40·0	43·0	46·5	48·5	53·0	44·5
10	40·0	44·0	43·5	48·0	50·0	54·0	57·0	63·0	56·5
11	42·5	46·0	49·0	51·0	54·0	57·0	60·5	61·5	59·0
14	40·5	45·5	50·0	56·0	61·5	68·0	74·5	78·5	71·0
15	44·0	45·5	45·5	48·5	50·5	54·0	59·5	65·0	59·0
19	47·0	45·5	41·5	45·5	46·5	48·0	51·0	54·0	49·5
22	42·0	44·5	47·5	50·0	52·0	57·5	61·5	66·0	59·5
24	38·5	42·0	46·0	48·0	52·0	55·5	58·5	61·5	59·5
26	39·0	39·5	37·5	39·5	41·5	45·5	48·0	53·0	48·0
30	41·5	41·0	42·0	45·5	50·5	56·5	62·5	65·5	62·0
Totals	411·5	432·0	440·0	472·0	501·5	542·5	581·5	621·0	568·5
Averages	41·2	43·2	44·0	47·2	50·2	54·2	58·2	62·1	56·8

TABLE VIII.

Group VIII.

Sheep No.	25.3.35.	22.4.35.	20.5.35.	18.6.35.	16.7.35.	12.8.35.	9.9.35.	7.10.35.	4.11.35.
1	41·5	45·0	44·5	49·5	50·0	53·0	55·0	60·5	54·5
2	46·0	54·0	52·5	58·5	63·5	70·5	76·0	79·0	74·0
5	38·5	42·0	47·0	52·0	55·0	57·5	63·5	69·0	65·0
8	37·5	39·5	41·0	44·0	45·5	51·5	54·5	59·5	56·0
12	41·0	41·0	40·0	42·5	44·5	47·5	52·0	55·0	48·5
16	42·5	44·0	41·5	43·5	44·0	47·5	48·0	53·5	50·5
20	47·0	54·5	56·0	62·0	66·0	68·5	73·0	76·5	71·5
23	40·0	44·5	47·5	54·0	58·0	60·5	68·5	70·0	63·5
27	37·0	40·5	41·5	46·5	50·0	53·0	56·5	57·5	55·5
28	41·0	41·5	40·5	44·0	45·5	48·5	52·0	52·5	49·0
Totals	412·0	446·5	452·0	496·5	522·0	558·0	599·0	633·0	588·0
Average	41·2	44·6	45·2	49·6	52·2	55·8	59·9	63·3	58·8

TABLES IX–XVI: OESTROUS OBSERVATIONS.

APPENDIX 6. **TABLE IX.** *Group I.* **EXPERIMENT 7.**

Sheep No.	Occurrences of oestrus.									No. of dioestrous cycles.	Period of sexual inactivity.	
	17th March.	April.	May.	June.	July.	Aug.	Sept.	Oct.	15th Nov.		Prior to onset of sexual season.	Subsequent to termination of sexual season.
											Days.	Days.
41629	—	—	—	—	—	—	—	—	—	0	—	244
41641	—	—	—	—	—	—	—	—	—	0	—	244
41647	—	—	—	—	—	—	—	—	—	0	—	244
41648	—	—	—	—	—	—	—	—	—	0	—	244
42393	—	—	—	—	—	—	—	—	—	0	—	244
42394	—	—	—	—	—	—	—	—	—	0	—	244
42396	—	—	—	—	—	—	—	—	—	0	—	244
42397	—	—	—	—	—	—	—	—	—	0	—	244
42398	—	—	—	—	—	—	—	—	—	0	—	244
42399	—	—	—	—	—	—	—	—	—	0	—	244

TABLE X. *Group II.*

Sheep No.	17th March.	April.	May.	June.	July.	Aug.	Sept.	Oct.	15th Nov.	No. of dioestrous cycles.	Prior to onset of sexual season.	Subsequent to termination of sexual season.
41624	—	—	—	—	—	—	—	—	—	0	—	244
41625	—	—	—	—	—	—	—	—	—	0	—	244
41630	—	—	—	—	—	—	—	5	—	1	202	41
41632	—	—	8,	5, 25	—	—	—	—	—	3	52	143
41639	—	—	—	—	—	—	—	—	—	0	—	244
41640	—	—	—	—	—	—	—	—	—	0	—	244
41642	—	—	—	—	—	—	—	—	—	0	—	244
41650	—	—	—	—	—	—	—	—	—	0	—	244
41652	—	—	—	—	—	—	—	—	—	0	—	244
42395	—	—	—	—	—	—	—	—	—	0	—	244

TABLE XI. *Group III.*

Sheep No.	17th March.	April.	May.	June.	July.	Aug.	Sept.	Oct.	15th Nov.	No. of dioestrous cycles.	Prior to onset of sexual season.	Subsequent to termination of sexual season.
41623	—	—	—	—	—	—	—	—	—	0	—	244
41626	—	—	—	—	—	—	—	—	—	0	—	244
41627	—	—	—	—	—	—	—	—	—	0	—	244
41628	—	—	—	—	—	—	—	—	—	0	—	244
41635	—	—	—	—	—	—	—	—	—	0	—	244
41638	—	—	—	—	—	—	—	23	—	1	220	23
41644	—	—	13,	—	—	—	—	—	—	1	57	186
41645	—	—	—	—	—	—	—	—	—	0	—	244
41649	—	—	—	—	—	—	—	—	—	0	—	244
42392	—	—	—	—	—	—	—	—	—	0	—	244

OESTROUS OBSERVATIONS—(*continued*).

APPENDIX 6. TABLE XII. *Group IV.* EXPERIMENT 7.

Sheep No.	Occurrences of oestrus.									No. of dioestrous cycles.	Period of sexual inactivity.	
	17th March.	April.	May.	June.	July.	Aug.	Sept.	Oct.	15th Nov.		Prior to onset of sexual season.	Subsequent to termination of sexual season.
											Days.	Days.
41633	—	—	—	—	—	—	—	—	—	0	—	244
41634	—	—	2, 19	—	—	—	—	—	—	2	46	80
41636	—	—	15,	—	—	—	—	—	—	1	59	184
41637	—	—	—	—	—	—	—	—	—	0	—	244
41631	—	—	—	1,	—	—	—	—	—	1	74	167
41643	—	—	—	—	—	—	—	—	—	0	—	244
41646	—	—	—	—	—	—	—	—	—	0	—	244
41651	—	—	—	—	—	—	—	—	—	0	—	244
42390	—	—	—	—	—	—	—	—	—	0	—	244
42391	—	—	—	—	—	—	—	—	—	0	—	244

TABLE XIII. *Group V.*

Sheep No.	17th March.	April.	May.	June.	July.	Aug.	Sept.	Oct.	15th Nov.	No. of dioestrous cycles.	Prior to onset of sexual season.	Subsequent to termination of sexual season.
M1	—	1st. ,18	5, 23	11, 28	—	—	—	—	—	5	17	140
M2	—	—	—	—	—	—	—	—	—	0	—	229
M3	—	—	,23	—	—	—	—	—	—	1	52	176
M4	—	,26	15,	1,	—	—	—	—	—	3	25	167
M5	—	14, 22	2, 15, 26	13,	12,	—	—	—	—	7	13	126
M6	—	—	—	—	—	—	—	—	—	0	—	229
M7	—	—	—	—	—	—	—	—	—	0	—	229
M8	—	,23	10, 29	,16	—	—	—	—	—	4	22	152
M9	—	—	—	—	—	—	—	—	—	0	—	229
M10	—	—	—	—	—	—	—	—	—	0	—	229

TABLE XIV. *Group VI.*

Sheep No.	17th March.	April.	May.	June.	July.	Aug.	Sept.	Oct.	15th Nov.	No. of dioestrous cycles.	Prior to onset of sexual season.	Subsequent to termination of sexual season.
3	—	8th. —	—	—	—	—	—	—	—	0	—	222
4	—	—	—	—	—	—	—	—	—	0	—	222
6	—	—	—	—	—	—	—	—	—	0	—	222
9	—	—	—	—	—	—	—	—	—	0	—	222
13	—	—	—	—	—	—	—	—	—	0	—	222
17	—	—	—	—	—	—	—	—	—	0	—	222
18	—	—	—	,25	12, 30	,17	—	—	—	4	78	90
21	—	—	—	,22	—	—	—	—	—	1	75	146
25	—	—	—	—	—	—	—	—	—	0	—	222
29	—	—	—	—	—	—	—	—	—	0	—	222

OESTROUS OBSERVATIONS—(*continued*).

APPENDIX 6. **EXPERIMENT 7.**

TABLE XV. *Group VII.*

Sheep No.	Occurrences of oestrus.									No. of dioestrous cycles.	Period of sexual inactivity.	
	March.	8th April.	May.	June.	July.	Aug.	Sept.	Oct.	15th Nov.		Prior to onset of sexual season.	Subsequent to termination of sexual season.
											Days.	Days.
7	—	—	—	—	—	—	—	—	—	0	—	222
10	—	.28	15,	—	—	—	—	—	—	2	20	184
11	—	—	—	—	—	—	—	—	—	0	—	222
14	—	.28	15,	—	—	—	—	—	—	2	20	184
15	—	—	—	—	—	—	—	—	—	0	—	222
19	—	,18	5, 23	9,	15,	—	—	—	—	5	10	123
22	—	—	—	—	—	—	—	—	—	0	—	222
24	—	—	—	.25	11, 29	—	—	—	—	3	78	109
26	—	—	—	—	—	—	—	—	—	0	—	222
30	—	—	—	—	—	—	—	—	—	0	—	222

TABLE XVI. *Group VIII.*

1	—	—	,19	,25	,13	—	—	—	—	3	41	125
2	—	—	—	—	—	—	—	—	—	0	—	222
5	—	—	—	—	—	—	—	—	—	0	—	222
8	—	—	—	—	—	—	—	—	—	0	—	222
12	—	—	—	—	—	—	—	—	—	0	—	222
16	—	—	—	—	—	—	—	—	—	0	—	222
20	—	—	,15	,23	—	—	—	—	—	2	37	145
23	—	—	—	—	—	—	—	—	—	0	—	222
27	—	—	—	—	—	—	—	—	—	0	—	222
28	—	—	—	—	—	—	—	—	—	0	—	222

APPENDIX 7.

EXPERIMENT 8.

TABLES I–VI.—WEIGHTS OF SHEEP IN POUNDS.

TABLE I.

Group I.

Sheep No.	1933.						1934.								
	13.10.	27.10.	9.11.	25.11.	9.12.	23.12.	6.1.	20.1.	2.2.	17.2.	3.3.	17.3.	29.3.	14.4.	28.4.
15363	86·0	90·5	89·5	93·5	95·0	97·0	95·5	98·5	101·5	103·5	95·0	97·0	96·5	97·5	95·5
21469	64·0	72·5	76·5	76·5	78·5	81·0	81·0	84·0	88·5	87·0	82·0	82·0	81·5	83·0	83·0
21544	66·0	72·0	77·0	77·5	80·5	83·5	89·0	89·5	90·5	84·5	74·5	80·5	77·5	81·5	80·5
21566	66·0	74·5	80·0	78·5	79·0	79·5	83·5	83·0	85·0	83·0	71·5	77·5	77·0	78·5	76·0
25956	73·0	82·0	87·0	92·0	95·5	96·0	99·5	101·0	105·5	102·0	95·5	98·0	98·0	99·5	101·0
25957	68·0	77·5	78·0	75·5	82·0	85·0	85·5	85·5	91·5	90·5	84·0	87·5	84·0	84·0	88·5
32935	64·0	71·0	76·5	75·5	79·0	83·5	87·5	84·0	90·5	89·5	82·0	87·0	87·0	88·0	87·0
35728	48·5	57·5	57·0	57·5	58·5	64·0	68·0	66·0	67·5	68·0	64·5	62·5	61·0	63·0	62·5
35969	68·0	73·0	79·5	78·5	78·5	81·5	87·0	86·0	90·0	91·0	89·0	85·5	85·0	87·0	84·0
37066	73·0	82·0	87·5	85·0	87·0	92·0	98·0	97·0	102·0	98·5	92·5	92·5	92·0	92·0	93·5
Totals	676·5	752·5	788·5	790·0	813·5	843·0	874·5	874·5	912·5	897·5	830·5	850·0	839·5	854·0	851·5
Averages	67·6	75·2	78·8	79·0	81·4	84·3	87·4	87·4	91·2	89·8	83·0	85·0	84·0	85·4	85·2

TABLE II.

Group II.

15364	70·0	80·5	83·0	87·5	84·0	89·5	90·5	90·5	98·0	100·0	100·0	101·0	99·0	99·5	99·0
22086	64·0	67·5	70·0	70·5	66·5	72·5	74·5	74·0	77·5	76·0	75·5	77·0	77·0	76·5	77·5
25027	68·5	74·0	75·5	75·5	74·5	79·0	80·5	78·5	82·0	80·0	83·0	86·5	84·5	85·5	83·5
25034	64·0	66·5	73·5	73·5	67·0	74·0	80·0	76·5	82·0	84·5	82·0	84·5	84·0	86·0	84·0
25072	68·0	74·5	78·0	74·5	70·0	75·0	78·5	77·0	78·5	79·0	78·0	78·5	78·5	78·0	78·5
25082	50·5	55·0	58·0	57·5	55·0	57·5	62·5	60·0	64·0	61·5	65·0	65·5	61·0	64·0	64·0
35981	84·5	90·5	94·0	95·0	90·5	95·0	101·0	101·0	103·0	105·5	103·5	104·5	104·0	107·5	105·0
35982	73·0	78·0	79·5	80·5	75·0	79·0	83·0	79·5	85·0	84·0	84·0	86·0	86·0	86·0	86·0
37065	65·5	76·5	79·5	81·0	79·5	84·0	88·0	85·5	88·5	90·0	88·0	90·5	88·0	89·5	91·5
38531	66·0	74·0	80·0	79·5	73·5	81·0	83·0	81·0	87·5	86·0	82·5	85·5	84·0	84·5	83·5
Totals	677·0	737·0	771·0	775·0	735·5	786·5	821·5	802·5	846·0	846·5	841·5	859·5	846·0	857·0	853·0
Averages	67·7	73·7	77·1	77·5	73·6	78·6	82·2	80·2	84·6	84·6	84·2	86·0	84·6	85·7	85·3

WEIGHTS OF SHEEP IN POUNDS—(*continued*).

APPENDIX 7. TABLE III. *Group III.* **EXPERIMENT 8.**

Sheep No.	1933.						1934.								
	13.10.	27.10.	9.11.	25.11.	9.12.	23.12.	6.1.	20.1.	2.2.	17.2.	3.3.	17.3.	29.3.	14.4.	28.4.
25878	74·5	82·5	91·5	91·0	89·5	91·5	96·0	95·0	95·0	97·0	95·0	97·0	96·5	93·5	94·0
25925	66·5	71·0	75·0	74·0	72·5	75·5	77·5	75·5	80·5	82·0	83·0	80·0	82·0	84·0	79·5
25926	58·0	66·5	67·0	67·0	67·5	74·0	75·0	76·0	72·5	69·5	75·0	75·5	72·0	73·5	75·5
25930	72·0	75·0	79·5	84·0	76·0	84·0	86·0	87·0	92·5	91·0	91·0	93·0	91·5	94·0	91·5
26243	68·0	76·0	80·5	83·5	79·0	83·0	86·5	84·5	89·5	89·0	92·5	92·0	91·5	91·0	89·0
35596	63·5	70·0	73·5	70·0	64·5	72·5	69·5	70·5	74·5	71·5	77·0	77·5	75·0	75·0	75·5
25645	65·5	70·0	72·0	73·5	65·5	73·0	77·5	77·0	77·5	75·5	77·5	80·0	73·0	72·5	72·0
35965	64·5	71·0	72·5	70·5	70·0	73·5	73·0	74·0	79·0	76·5	79·0	77·5	78·5	79·0	77·0
37067	69·0	75·0	78·5	83·0	79·5	85·5	90·5	88·5	92·0	92·0	90·5	92·0	93·0	93·0	91·0
38532	83·5	87·5	89·5	88·5	85·5	89·5	92·0	88·0	93·5	93·0	95·0	96·5	97·0	94·0	94·0
Totals	685·0	744·5	779·5	795·0	749·5	802·0	823·5	816·0	846·5	837·0	855·5	861·0	850·0	849·5	839·0
Averages	68·5	74·4	78·0	79·5	75·0	80·2	82·4	81·6	84·6	83·7	85·6	86·1	85·0	85·0	83·9

TABLE IV. *Group IV.*

Sheep No.	13.10.	27.10.	9.11.	25.11.	9.12.	23.12.	6.1.	20.1.	2.2.	17.2.	3.3.	17.3.	29.3.	14.4.	28.4.
15426	63·0	69·0	73·5	71·0	73·0	78·5	82·5	80·0	83·5	83·5	78·5	80·0	79·0	81·0	79·5
21619	71·5	80·5	83·0	82·5	84·5	88·0	90·5	87·0	89·0	90·5	82·0	85·0	80·5	84·0	85·5
24247	81·0	86·5	85·0	88·0	85·0	96·5	99·5	99·0	99·5	94·0	86·5	94·5	92·0	94·0	94·0
25915	70·0	71·0	80·0	78·5	82·0	88·0	88·0	87·5	91·5	89·0	85·0	83·5	84·5	86·5	84·0
32490	59·0	63·0	66·0	64·0	65·0	65·5	70·5	65·0	67·0	70·5	64·5	68·5	68·5	66·0	70·0
33015	65·5	71·0	75·5	74·5	76·5	79·0	83·5	80·5	83·0	81·5	76·5	78·0	74·0	76·5	76·0
35970	67·5	67·0	75·5	72·5	75·5	81·5	82·0	79·0	85·5	84·5	75·0	82·0	83·0	82·5	83·5
36005	74·5	79·0	83·0	84·0	87·0	86·0	91·0	87·0	94·5	91·5	84·5	90·5	87·5	87·0	88·0
36007	64·5	69·0	—	72·0	76·0	79·5	81·0	82·0	88·5	88·5	82·5	86·5	82·0	83·5	85·0
36013	68·5	75·0	81·0	72·5	78·0	85·5	91·0	85·5	91·5	89·5	82·0	86·5	84·0	82·0	85·5
Totals	685·0	731·0	702·5	759·5	782·5	828·0	859·5	832·5	873·5	840·0	797·0	835·0	815·0	823·0	831·0
Averages	68·5	73·1	78·0	76·0	78·2	82·8	86·0	83·2	87·4	84·0	79·7	83·5	81·5	82·3	83·1

WEIGHTS OF SHEEP IN POUNDS—(*continued*).

APPENDIX 7. TABLE V. *Group V.* EXPERIMENT 8.

Sheep No.	1933.						1934.								
	13.10.	27.10.	9.11.	25.11.	9.12.	23.12.	6.1.	20.1.	2.2.	17.2.	3.3.	17.3.	29.3.	14.4.	28.4.
22014	70·5	72·0	78·0	75·5	79·0	86·5	89·5	89·5	92·5	93·0	82·5	83·5	84·0	85·6	86·5
22024	61·5	66·5	69·0	67·5	68·5	83·0	76·5	76·5	80·0	81·5	75·0	78·5	75·0	78·0	78·5
22050	65·0	78·0	82·5	85·0	83·5	94·0	94·0	90·0	94·5	95·5	90·0	94·0	91·0	93·5	91·0
25932	75·0	82·0	87·0	88·0	90·5	92·5	93·0	97·5	102·0	98·5	90·0	94·0	93·0	97·0	93·5
25950	70·5	73·5	77·0	74·5	80·5	83·5	87·0	88·0	92·0	93·0	93·0	86·0	85·5	87·5	88·5
26302	76·0	82·0	96·0	88·0	94·0	98·0	97·0	97·0	100·0	102·0	93·0	96·0	93·0	95·0	96·5
29250	67·5	66·0	73·5	73·5	78·0	79·0	85·0	83·5	87·5	88·0	82·0	83·0	—	73·0	75·0
35973	62·5	67·5	70·5	69·0	71·0	75·0	75·0	77·0	81·5	82·0	76·5	73·5	76·0	79·0	78·5
35984	67·5	75·5	75·0	79·0	79·0	83·5	89·0	87·0	89·0	90·5	83·5	85·5	85·0	83·0	84·0
38530	64·5	69·0	68·0	65·5	68·5	72·5	72·0	74·5	77·5	78·5	66·5	72·0	73·0	76·0	74·5
Totals	680·5	731·5	766·5	765·5	792·5	837·5	858·0	860·5	896·5	902·5	822·0	846·0	755·5	848·5	846·5
Averages	68·0	73·2	76·6	76·6	79·2	83·8	85·8	86·0	89·6	90·2	82·2	84·6	83·9	84·8	84·6

TABLE VI. *Group VI.*

Sheep No.	13.10.	27.10.	9.11.	25.11.	9.12.	23.12.	6.1.	20.1.	2.2.	17.2.	3.3.	17.3.	29.3.	14.4.	28.4.
15360	—	—	—	106·5	99·5	104·5	108·5	109·5	111·0	110·0	109·0	110·5	110·0	109·5	108·0
21434	—	—	—	79·5	73·0	79·0	80·5	82·5	87·5	84·5	84·5	84·0	84·0	86·0	86·0
35568	—	—	—	63·5	60·5	61·5	64·5	64·5	68·0	64·0	64·0	64·0	65·0	64·0	64·5
35631	—	—	—	80·0	73·5	77·0	78·0	74·0	77·0	76·0	78·0	75·5	73·0	74·5	74·0
35570	—	—	—	92·0	85·0	86·0	89·5	89·0	88·0	89·0	88·0	91·5	87·0	86·5	82·5
35571	—	—	—	91·0	82·0	83·5	87·0	87·5	91·5	86·0	89·0	90·5	90·0	90·5	89·5
35585	—	—	—	86·0	77·0	82·0	85·5	80·0	82·0	82·5	85·0	83·0	82·5	84·0	82·5
35578	—	—	—	67·5	63·0	70·5	74·0	71·5	77·5	73·0	78·0	80·0	78·5	81·0	79·5
35703	—	—	—	72·0	65·0	70·0	70·5	69·0	74·0	72·0	71·5	72·5	71·5	71·0	72·0
35888	—	—	—	86·5	82·0	86·5	89·0	85·5	93·0	92·5	92·5	92·0	90·0	93·5	93·0
Totals	—	—	—	824·5	760·5	800·5	827·0	817·0	849·5	829·5	839·5	844·5	831·5	840·5	831·5
Averages	—	—	—	82·4	76·0	80·0	82·7	81·7	85·0	83·0	84·0	84·4	83·2	84·0	83·2

APPENDIX 7A.

EXPERIMENT 8.

MACROSCOPIC EXAMINATION OF THE OVARIES OF INACTIVE SHEEP.

(1) *Sheep No.* 35645.—Date slaughtered, 15th August, 1934; age, 6 years; condition, fair; weight, 81·0 lb.

Sexual History.—No exhibition of oestrus was observed during the testing period, 13th October, 1933, to 5th October, 1934.

Left Ovary.—Weight, 0·55 gm.; measurements, 1·5 by 0·9 by 0·7 cm.

Only two small Graafian follicles with diameters of 0·1 and 0·2 cm. are seen near the surface of the ovary.

No corpus luteum is present but some remnants of previous corpora lutea are seen.

Right Ovary.—Weight, 0·81.; measurements, 1·6 by 1·1 by 0·9 cm.

One large Graafian follicle with a diameter of 0·5 cm. is seen on a pole of the ovary, while numerous smaller follicles are present.

No corpus luteum is present but many remnants of previous corpora lutea are seen.

(2) *Sheep No.* 35965.—Date slaughtered, 22nd June, 1934; age, 6 years; condition, fair; weight, 75·0 lb.

Sexual History.—No exhibition of oestrus was observed during the period of testing, 13th October, 1933, to 22nd June, 1934.

Left Ovary.—Weight, 0·66 gm.; measurements, 1·3 by 1·0 by 0·6 cm.

Numerous small Graafian follicles are seen, the largest of which is 0·3 cm. in diameter.

A cone shaped corpus luteum measuring 0 9 by 0·7 cm. is present. The corpus has been sectioned and it is found to have a cavity 0·3 cm. in diameter. The remnants of previous corpora lutea occur as dark brown specks.

Right Ovary.—Weight, 0 61 gm.; measurements, 1·3 by 1·0 by 0·6 cm.

Three Graafian follicles varying in size from 0·4 to 0·1 cm. are seen.

A corpus luteum in the form of a complete circular ball 0·6 cm. in diameter is found attached to and entirely outside the ovary. Externally the colour of the body is cream and on section the colour of the cut surfaces is somewhat lighter. This is apparently a corpus luteum of the previous interovulation period somewhat abnormally situated.

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Researches into Sterility of Cows in South Africa.

The Influence of: (i) Dry Rations, (ii) Lack of Exercise, and (iii) Lack of Sunlight on Reproduction in Beef Heifers and Cows.

By JOHN QUINLAN and LUCIEN L. ROUX, Section of Surgery, Gynaecology and Radiology, Onderstepoort.

In a previous publication, Quinlan (1929) published a report of his researches into sterility of cows in South Africa. That report covered investigations into the local pathological genital causes of sterility as observed under the environmental conditions prevailing in South Africa. The histological anatomy of the diseased genital organs of a number of cows was studied after the clinical pathology had been examined periodically over a period of months. The therapeutic measures adopted to overcome pathological genital lesions were described. An attempt was made to ascertain whether there were concurrent ductless glands and genital pathology in permanently sterile cows by making a macroscopic and histological study of the hypophysis, epiphysis, thymus, thyroid, and adrenal glands.

Since the publication of the above-mentioned work, observations have been made on certain factors which are popularly associated with the aetiology of low fertility in cattle. The object of some of these observations was to ascertain the effects of continuous dry rations on reproduction in beef cattle, when fed in such quantities as to produce condition better than that usually associated with the ideal for normal genital physiology.

Since the experimental issue could be broadened by restriction of exercise and restriction of exposure to the sun's rays, the influence or inactivity and darkened stalls on reproduction was studied concurrently.

The close relationship between nutrition and normal functioning of the genitalia of cattle has been indicated by the foremost authorities on genital pathology. The importance of a correctly balanced ration, containing a sufficiency of vitamins A, B, C, D, and E, to maintain physical and genital fitness is emphasised if the highest fertility is to be attained: Williams (1921, '32), Richter (1926), Wester (1921), Zschokke (1900), Oppermann (1922), Albrechtsen (1917), Nielsen (1926), Hammond (1927, '33), Stalfors (1930), Korenchevsky (1933), *et al.* In fact, all workers who have discussed the causation of low fertility in a general way have stressed the probability of constitutional aetiology due to errors in diet.

The association of unsuitable environmental conditions outside the nutritional aspect has long been known to be incompatible with the highest fertility. Hammond (1933) points out that lack of exercise and dry rations are not conducive to regular breeding. He also indicates that, by analogy with experiments done on ferrets, the ripening of the ovum is delayed by the shortening hours of daylight, just as fowls lay fewer eggs in autumn unless they are lighted and fed high protein foods with salts. Inhygienic housing, obesity, malnutrition, lack of exercise, feeding for forced milk production, and controlled breeding with the object of prolonging lactation, are factors which must be considered artificial and which tend to cause a deviation from normal physiological genital activity. Similarly too, early breeding, and careless management during calfhood have been inculpated as aetiological factors. Williams (1932) stresses the detrimental influence on the subsequent breeding records of heifers bred too young. Withycombe, Potter and Edwards (1930) have shown that calving at the age of two years reduced the percentage of calves produced by the same cows at the ages of three and four, but not at the ages of five and six. There is no questioning the detrimental influence of vitamin deficiencies in diet on the gonads: Korenchevsky (1933), Sampson, Dennison, and Korenchevsky (1932), Sampson and Korenchevsky (1932), Siperstein (1921). Roux (1936) has shown that when sheep are maintained on low-level rations for extended periods of time, follicular development is inhibited and the number of follicles present in the ovaries is greatly reduced.

An immense literature has been published on this aspect in laboratory animals within recent years. This is, however, outside the scope of this paper and will not be reviewed in detail.

Genetic tendency to difficult breeding in association with any of the above factors appears to exaggerate the difficulty.

It is realised that unsuitable food or lack of food, unsuitable conditions of hygienic environment, and sex hygiene will detrimentally influence the physical well-being of cattle so that general constitutional causes will favour local genital infection.

The present article is not concerned with this aspect of infertility. Local genital causes, the result of infections following on lowered vitality, have been previously dealt with (Quinlan, 1929). The object of the present work is to record the behaviour of the genital tract of beef heifers and cows, when placed in an environment enforcing some factors which are popularly associated with low fertility: The factors considered are lack of sunlight, lack of exercise, dry rations, and high condition.

Usually insufficiency of light and exercise are associated with unhealthy stabling and general bad management, but in this experiment these associated hygienic factors can be ruled out.

The precise causes of reproductive failure in many cases of so-called functional sterility or infertility are obscure. Few references can be found in the literature on sterility of cattle to indicate that there are any experimental data on the influence of lack of exercise, lack of sunlight, and lack of green food on cattle. The object of the present experiment was to try and assemble data on these points.

It appears to be true that any factor which causes a deviation from ideal breeding condition or what is visualised as ideal breeding condition, will tend to lessen the bovine birth-rate. It is highly probable, however, in view of the results which will be discussed in this paper, that some secondary concurrent factors are necessary to cause that deviation in sex-physiology which produces difficult breeding in cattle fed on dry rations and showing obesity, or those which are housed under conditions enforcing restriction of exercise and sunlight.

The immediate causes of erratic behaviour of the genital tract appear to lie in the functioning of the internal secretory glands, most probably the ovary and the pituitary [Parkes (1933), Cole and Miller (1933), Fairlie (1935), Zavadovskii, Wunder, Paduceva, and Margvelasvili (1935), Cole and Miller (1935), *et al*].

From observations made on the ductless glands of cattle by Quinlan (1929), there would appear to be no constant histological change in these glands in cases of so-called functional sterility. The change appears to be in function not in structure. Further, it appears that return to normal can take place quickly when ideal conditions are restored.

Parkes (1933) states that the absence of antipituitary hormone causes the ovary to degenerate so far as appreciable follicles are concerned, but even in long standing hypophysectomies normal primordial ova, surrounded by one or more layers of follicular epithelium, are still found. This indicates that the ovary requires only the necessary stimulation to awaken normal function. Cole and Miller (1933) and Zavadovskii, *et al.* (1935), have shown that normal oestrus and ovulation can be produced in sheep by injections of the gonad stimulating hormone during anoestrum. However, the more recent work of Cole and Miller (1935) upon sheep during anoestrum, with oestrin and gonadotropic hormone indicates that, while the former is effective in producing oestrus and while ovulation is induced by the latter hormone, the simultaneous administration of the two hormones does not result in a combination of effects. Hill and Parkes (1931) (1933) have shown that the ovary may remain normal during enforced quiesence in hypophysectomised rabbits. Quin (1935) injected eight sheep in a state of anaphrodisia, which had not shown oestrus for 12 months, with oestrin from stallion's urine and obtained 50 per cent. fertility from mating during the oestrus following injection.

These data show that, although there may be a prolonged ovarian quiescence, or absence of the psychological phenomena associated with oestrus, the ovary needs only the necessary stimulation to resume normal physiological activity. It appears, however, that at least in some cases of prolonged quiescence in cattle, in other words delayed breeding, either from withholding service or from the absence of normal oestrus, there is a tendency to difficult breeding. Quinlan (1929) has seen degenerative atrophy of the uterine mucosa in purebred imported heifers of the beef breeds, which were retained for some years as virus-reservoirs for red-water and gallsickness vaccine. Some of the cows actually failed to breed when eventually mated, while others conceived but aborted during the early weeks of pregnancy.

Forced milk-production under the environmental conditions and the usual methods of nutrition adopted to obtain high milk-yields, act upon the oestrogenic mechanism. The demand made upon the animal system is, in many cases, reflected on the genital tract. Very heavy milking cows may not show the psychological symptoms of oestrus. This has been shown in the case of the rabbit by Hammond (1930).

In South Africa, where the nutritional and general environmental conditions are inadequate to allow high inherited milk-yields from finding full expression, these genetical potentialities constitute limiting factors in regular breeding.

The question of functional sterility of dietetic origin is of more than ordinary interest in South Africa, where in certain localities the veld grazing is definitely deficient in phosphates and for the greater part of the year there is protein deficiency in addition. In those areas the bovine birth rate is abnormally low. From observations made at the Veterinary Research Station at Armoedsvlakte, Vryburg, it has been seen that failure to breed is due to failure to conceive during what appears to be normal oestrum and also to temporary anaphrodisia which may extend over a period of months (Bisschop, 1935).

In experimental observations at Onderstepoort, in which the mineral content of the ration was carefully measured and was definitely sub-optimum, and in further experiments made on a herd running on Armoedsvlakte veld, it has been shown that there is a low bovine birth rate and that abnormal calves showing weakness and congenital amaurosis are born [Theiler, Green, and du Toit (1927); du Toit and Bisschop (1929); du Toit and Malan (1934; Theiler (1933)]; Bekker (1932) showed the detrimental influence of phosphorus deficiency on reproduction in ewes grazing on Armoedsvlakte veld. The addition of bone meal to the diet improved fertility. Roux (1936) has shown that the liberal feeding of bone meal, as opposed to its absence, ensures greater sexual activity in sheep, although individual differences are not entirely eliminated; the duration of the sexual season is prolonged by an increased number of dioestrous cycles being experienced, and by the number of dioestrous cycles of abnormal duration being reduced.

Greatest sexual activity was obtained by supplementing the natural pasture with green grazing and a mineral lick throughout the year. Individual differences are considerably lessened by such treatment.

Whetham (1933) has drawn attention to the influence of the duration of light on egg production in the fowl. Hammond (1933) says, "It is supposed that light stimulates the anterior-pituitary by way of the eye and that in autumn, with decreasing daylight, fowls with a genetically low level of anterior-pituitary will fall below the critical level for egg production and so sterility from this cause will result. It is during the autumn and winter months that the low producing strains cease laying. In some animals very much the same sort of thin occurs: Ferrets, which do not normally ripen ova during the autumn and winter months, may be made to do so by giving them electric light after dark (Bissonette, 1932). We can assume, therefore, that the genetic constitution of the ferret is such that its pituitary activity is dependent upon light stimulation". Hill and Parkes (1934) have confirmed the effect of illumination with electric light in producing oestrus in the female ferret.

Hammond (1933) further suggests that it is probably the change in the light ration, not the actual amount, which is the cause of pituitary stimulation, as most breeds of sheep in England ripen ova with declining sunlight in September and cease with increasing daylight in February.

This suggestion of Hammond would appear to show that if light, as a stimulating factor to the anterior pituitary, is sufficient an increase of the intensity of light will not influence it further. This is borne out by our observations on the ovarian activity of sheep on the high veld in this country. In November and December, during the warmest and longest days of the South African summer, ovarian activity in sheep is at its lowest. Further, the veld nutrition is usually at its best at this time.

Marshall (1932) indicates that the response of different animals to light must vary greatly, as some animals have no restricted breeding period even in temperate zones. Llewellyn (1932), quoting Cook (1894), states that in North Greenland evidence of sexual periodicity exists in the Eskimos. At the onset of winter, sexual desire fails and menstruation during the winter months is absent. Sexual activity again reawakes in the spring. Llewellyn indicates that the hiatus in the sexual cycle is due to absence of sunlight, that light and heat rays seem essential for the maintenance of the sexual cycle. He suggests that this is a species of hibernation localized to the hypophyso-gonadal system. The suggestion that it is a rare peculiarity is denied by Cook, since he states that their own party suffered from muscular debility in a similar manner to the Eskimos.

Hogan (1932) made observations on the influence of direct sunlight on swine as compared with swine kept in indoor quarters. He come to the conclusion that there was no improvement in those which had access to sunlight.

The importance of light on the productive activity of certain voles and ferrets has been indicated by Baker and Ranson (1932) and Bissonnette (1931). According to Whetham (1933) "the mammalian female responds more completely than the male, the female fails to respond on a reduced supply of light, while the male appears to be unaffected and similarly with an increased light supply it is the female which responds more completely ".

Marshall and Bowden (1934) have indicated that light radiations of particular wave-lengths and sufficient intensity are an efficient cause of reproductive activity, but that the recurrence of the oestrous cycle is conditioned by other factors which, in the absence of variation in the daily duration of light, may play an important rôle.

Rowan (1925, 1929) maintains that it is muscular exercise rather than light that caused change in the gonads of birds, but Bissonnette (1931) showed that exercise was not essential. Stalfors (1930) indicates the necessity for open air for high production as well as a supply of vitamins A, B, C, and D for cattle.

The above literature is confined mostly to fowls and laboratory animals. There are no experimental data on the influence of light and exercise on the reproductive activity of cattle, horses, sheep, pigs, and dogs. It has been mentioned that lack of exercise, lack of sunlight, and lack of green feed have been associated with low fertility in cattle, but such conclusions have been based on circumstantial evidence without experimental proof.

Much work has been done on the influence of diet on fertility in laboratory animals [Hart, Steenbock, Humphrey, and McCallum 1911); Reynolds and Macomber (1920, 1921, 1924); Benedict (1911); Sure (1926); Simmonds, Becker, and McCallum (1927); Evans (1923); Evans and Bishof (1922); Evans and Burr (1927); Macomber (1927)]. It appears that, on a diet insufficient in calcium conception can take place, but the embryo dies early and is aborted. Moench (1931) says that, with the present-day diet in humans, sterility in women is unlikely to occur from that cause. He states that: " Diät und ihr Einfluss auf die Fruchtbarkeit zu eng begrenzt ist und dass wir anstatt nur von Diät lieber von dem allgemeinen Gesundheidszustande und seinem Bezug auf die Fertilität sprechen sollten. Ich halte den allgemeinen Gesundheitszustand in dieser Beziehung für äusserst wichtig und werde ich später bei dem Thema der Spermuntersuchung wieder darauf zuruckkommen. Leider wird aber oft gerades das Thema des allgemeinen Gesundheitszustandes recht stiefmütterlich behandelt und abgetan. Anstatt der Diät halte ish die köperliche Betätigung, die physiche arbeit die das Individuum leistet, für äusserst wichtig und glaube dass genügende Köperliche Bewegung ein sine qua non bester Gesundheit und damit auch guter Fertilität ist. Von der Diät braucht man, glaube ich, nur zu verlangen, dass sie ausreichend ist und dass sie keine wichtigen Insuffizienzen aufweist, die eine Avitamitose hervorrufen würedn ".

It will be seen that Moench stresses the necessity for exercise or physical work. He points out that, provided the diet is sufficient, work and exercise are more important factors in attaining the best health for normal sexual activity. In the case of obese women, he stresses the point that infertility is caused by too much food in relation to exercise. Obesity results in diminished circulation, oxidation, lessened blood to the ovary, and consequent subnormal ovarian activity. In these observations he is supported by Lahm (1927). Woodward (1920) has shown that the length of life of the bovine sperm can be raised by exercising the bull. This probably indicates greater chances of fertility under ordinary conditions of mating: that is where the sperm is not deposited in the vagina at the most favourable time for conception. Highly vital, long-lived sperm would probably survive longer in the genital tract of the female than less vital sperms [Quinlan, Maré, and Roux (1932, 1933)].

Guggisberg (?) indicated that the main object in a diet should be sufficiency in vitamin content, especially B, C, and E. In this connection, Moench states: "Dem kann ich aus eigener Erfahrung zustimmen. Es ist jedoch schwer, didaktische Regeln uber Diät und Fertilität aufzustellen—vieles ist noch gar nicht geklärt und bei manchen Fragen kommt man schliesslich wieder in das Gebiet des inneren Drüsensystems zurück"

The importance of dietetic errors and lack of exercise in infertility has been indicated by Orr and Fraser-Darling (1932). They associate these errors with unnatural and unhygienic environment and suggest that these factors may influence the normal physiology of the genitalia through the endocrine system and at the same time effect a reduction in the natural resistence to genital infection. These conclusions are arrived at after a critical review of the literature on the subject of sterility and infertility by a Committee of the Department of Agriculture of Scotland, comprising Mr. William Orr, M.R.C.V.S. and Dr. Fraser-Darling. The work contains an excellent bibliography on the subjects of physiological and genetical etiology of sterility in domestic animals by Miss N. V. Cytovich. Meigs and Converse (1933) have kept cows on grain and dry rations without pasture. They observed that, when the ration contained a liberal allowance of alfalfa hay of high feeding quality, the cows maintained their health and reproductive capacity up to more than seven years. When the roughage consisted of Timothy hay of bad quality, there was a definite lowering of the normal standard of health and the reproductive capacity of the cows was seriously interfered with. There was difficulty in conception and a marked tendency to throw off premature calves which were either dead, weak, or blind.

Hart, Steenbock and Humphrey (1920) observed that cows fed on a ration of grain and straw calved prematurely or threw dead or weak calves. This observation was confirmed by Huffman (1928) and Reed and Huffman (1925). The latter authors and Jones, Eckles and Palmer (1926) drew attention to the quality of Timothy hay as a highly important factor in genital functional activity of cattle. Copeland (1932) recorded a detrimental effect on reproduction in heifers fed on cotton seed hulls, as a sole dry roughage, when they were allowed to pasture for only six months in the year. Roux (1936) has observed marked sexual inactivity in sheep maintained on a carbonaceous roughage (teff hay) and a lick of bone meal and salt.

Hart and Guilbert (1928) and Webster (1935) have indicated the possible effects of phosphorus deficiency in cows under range conditions. The adverse influence of phosphate deficiency on reproduction in range cattle and sheep in South Africa has been shown by Theiler, Green, and du Toit (1927), Theiler (1933), and Bekker (1932).

Eckles, *et al.* (1935) showed that low phosphorus levels result in an upset of genital physiology, both in the oestrous cycle and reproduction in rats. They state that uncomplicated phosphorus deficiency did not influence the oestrous cycles of cattle. Oestrus was regular and not different from control animals of a like age. However, the breeding efficiency appeared to be reduced. They suggest that anaphrodisia is due to complicated deficiencies. They also state that a low phosphorus ration renders cows more susceptible to contagious abortion than those maintained on a normal diet.

Since there is also a protein deficiency during the greater part of the year on the range where these experiments were conducted, both factors must be considered in the etiology. Guilbert and Goss (1932) have indicated that protein levels of 3½ to 5 per cent. result in cessation of oestrus and long intervals between oestrus in the rat: further the rats failed to breed when mated.

Evans and Bisshop (1922) showed that protein deficiency decreases the percentage of normal oestrous cycles as well as the total number of cycles and that vitamin A deficiency greatly disturbs ovulation rhythm by prolonging the stage of cornified vaginal cells.

Cunningham and Hobkirk (1935) have induced sterility in male rats fed on diets of excessively high protein-content (65-82 per cent.), and also by feeding diets containing 15 to 18 per cent. protein. In the latter case a large part of the protein was derived from maize or maize and gelatine. All dietary constituents hitherto known to be essential for male fertility were included in the diets.

Roux (1936), working with ewes, obtained results indicating that the inclusion of a protein rich concentrate, cotton seed meal, in a low level carbonaceous ration and the exclusion of bone meal, causes a marked reduction of sexual activity, especially after eighteen months of treatment. The inclusion of the same protein rich concentrate in high level rations consisting of the same feeds, does not have this inhibiting effect.

Halverson and Sherwood (1930) showed that the feeding of cotton seed meal to cattle was associated with reproductive difficulties. Calves were born weak, and eye lesions were sometimes present. Hart, Guilbert and Goss (1932) have associated reproduction difficulties with lack of green food; at least the difficulty disappeared when green food became available. Infectious abortion was, however, present, but the authors concluded that there were data sufficient to lead them to suspect that feed deficiencies were the cause. Hart, Steenbock, Humphrey, and Hulce (1924) have shown the value of vitamin A, and calcium in obtaining normal reproduction in cattle. Fitch *et al.* (1932) showed that uncomplicated calcium deficiency did not lessen the breeding efficiency of a group of seven cows maintained on a calcium deficient ration for three years. Hogan (1932) indicates that rations for brood sows should contain not less than 0·4 per cent. of calcium.

Malan (1935) concludes from the results of his observations at Onderstepoort Laboratory that vitamin A deficiency in the ration of pregnant ewes and cows produces abortions or weakly young that are often blind and unable to rise. He observed, further, that the absence of this vitamin in the diet is in some ways associated with the absence of the psychological symptoms of oestrus. Both ewes and cows on dry rations containing a minimum of vitamin A show oestrus only very infrequently and even then, if mated will become pregnant only in a very small percentage of cases.

Lack of minerals such as phosphorus, the deficiency of which in the diet will produce clinical symptoms, has lead almost invariably in the Onderstepoort experiments on mineral metabolism to temporary infertility.

EXPERIMENTAL OBSERVATIONS.

The experiment was commenced on June 20th, 1929, when 27 grade Sussex-Afrikander heifers approximately fifteen months old were received at the Veterinary Research Laboratory and Experiment Station, Ermelo, Transvaal. The heifers were purchased from a private ranch in the western Transvaal; they were considered well grown and comparatively even with respect to type (Appendix, Figs. 1-18). Soon after their arrival at the Experiment Station they were divided at random into three groups, A, B, and C, and branded.

One heifer died two months after the commencement of the experiment. During the first six months, five heifers were found to be pregnant and they were withdrawn from the experiment; four of them were redrafted into the experiment about a year later.

A purchased Sussex bull was used in the experiment (Appendix I, Fig.19). The bull was bred by the School of Agriculture, Potchefstroom, Transvaal; it was two years old when transferred to the Ermelo Experiment Sation, and the serving of the heifers was commenced one month after his arrival, 17.10.30.

During the first month at the Experiment Station, the heifers were tested for tuberculosis, contagious abortion, and vaccinated against anthrax and quarter evil. Subsequently they have been retested for contagious abortion, and they have been tested annually for tuberculosis. The results of all tests were negative. The bull was tested annually for tuberculosis and contagious abortion; the results of the tests were negative. The bull was healthy and vigorous throughout the period of the experiment.

1. *Groups restricted in light and exercise: A and B.*

Stabling.—Groups A and B were housed in a wood-and-iron stable, 46 × 23 feet, with a cubic capacity of 8217 cubic feet. The stable was fitted with a double row of suitable mangers and hay racks, the heifers being fastened to the former by means of neck-halters and halter-chains. The two doors of the stable, each 4 × 6 feet 9 inches, opened to the east and to the west. The ventilation of the stable could be considered fair. Every endeavour was made to exclude light from the stable. Groups A and B can, therefore, be considered to have been housed in a dark stable and, but for the daily two watering periods of about twenty minutes each, these groups were confined to their stable day and night.

2. *Group not restricted in light and exercise*: *C*.

Group C was kept in a similar type of stable to that occupied by groups A and B. The dimensions of the stable were 46 × 15½ feet and cubic capacity 6328 cubic feet. It provided for a single row of cattle, the length ran from north to south, and a single 4 × 6 feet 9 inches door opened to the east. The ventilation of this stable was as good as, if not slightly better than, that occupied by the other two groups. The heifers in group C were fastened in a similar way to those in the other stable and they had similar mangers and hay racks.

In both stables each animal had a feeding space of 4½ feet. The floors of the stables were of flat stone. A native was in constant attendance keeping the floors clean and grooming the cattle; the latter were bedded down at night on the refuse of their roughage.

Management.—The feeding of the three groups was identical: the cattle were stall-fed, no green feed was given, and they were not put out on grazing.

At the commencement of the experiment the rations fed per capita per diem were:—

Crushed yellow maize: 4 lb.
Wheaten bran: 1 lb.
Teff hay: ad lib. (about 15 lb.).

As the heifers matured, the bran portion of the ration was increased to 2 lb. (per capita per diem) and the teff hay ration to 25-30 lb.

During three winter months, June, July, and August, maize silage was fed at the rate of 10-15 lb. per capita per diem and the hay ration was reduced.

The concentrate ration was fed dry, the ration of each cow being measured and fed in two equal portions daily. When silage was fed, the concentrate ration was mixed with the silage.

No minerals or mineral mixtures were fed to the animals during the course of the experiment.

The teff hay was fed in the hay racks twice daily.

Groups A and B received all their feed in the stable; Group C received the two concentrate rations and the evening hay ration in the stable, and the morning hay ration in an exercise yard 50 by 68 ft., in which this group was kept from 8.30 a.m. to 4.30 p.m. daily.

The following analyses of feeds used in the experiments have been extracted from the analyses given by Vipond (1914). The maize. ensilage and teff hay were analysed at Onderstepoort by S. J. Myburgh [S.Afr.(M.)]. In the case of the South African analyses of feeds, only the total percentages of feed constituents are given, whereas in the American analyses, the digestible percentages of feed constituents are also given.

Feed Analyses.

Feed.	Gm. per 100 gm. Feed.							
	Water.	Carotene mg/100 gm.	Crude Protein.	Carbo-hydrates.	Ether-soluble Extract (fat).	Crude Fibre.	Ash.	Phosphoric Oxide (P_2O_5).
Maize Flint [S. Afr. (V)]	8·6	—	11·0	72·3	5·0	1·7	1·4	0·6
Maize Flint (Amer.)	11·3	—	10·5	70·1	5·0	1·7	1·4	0·7
Wheat Bran [S. Afr. (V)]	11·0	—	19·2	54·2	2·5	7·0	6·1	1·7
Wheat Bran (Amer.)	13·0	—	14·0	56·0	4·0	9·0	4·0	2·7
Teff Hay [S. Afr. (V)]	8·2	—	6·0	43·1	1·1	34·8	6·7	0·2
Teff Hay [S. Afr. (M)]	5·9	1·6	8·0	—	—	26·8	6·3	0·3
Maize Silage [S. Afr. (V)]	75·7	—	2·3	10·9	0·8	8·4	1·9	0·44
Maize Silage [S. Afr. (M)]	73·7	0·4	2·6	—	—	5·8	2·7	0·47
Maize Silage (Amer.)	79·1	—	1·7	11·0	0·8	6·0	1·4	0·1

Feed.	Gms. per 100 gm. Feed.		Albuminoid Ratio in Total Percentage.	Gm. Digestible matter per 100 gm. Feed.				Albuminoid Ratio in Digestible Matter.
	Potash (K_2O).	Lime (CaO).		Protein.	Ether-soluble Extract (fat).	Carbo-hydrates and Fibre.	Starch Value.	
Maize Flint [S. Afr. (V)]	0·45	trace	7½	—	—	—	—	—
Maize Flint (Amer.)	0·4	·02	7¾	8·0	4·3	66·2	83	9½
Wheat Bran [S. Afr. (V)]	—	·13	3¼	—	—	—	—	—
Wheat Bran (Amer.)	1·5	0·2	4¾	10·0	3·0	45·0	47	5¼
Teff Hay [S. Afr. (V)	1·4	0·2	10¼	—	—	—	—	—
Teff Hay [S. Afr. (M)]	1·4	0·2	—	—	—	—	—	—
Maize Silage [S. Afr. (V)]	1·4	0·4	7	—	—	—	—	—
Maize Silage [S. Afr. (M)]	1·4	0·4	—	—	—	—	—	—
Maize Silage (Amer.)	0·4	—	8¾	0·9	0·7	11·3	11½	14¼

Groups A and B, which were kept in the dark stable, were restricted to a limited amount of exercise. These groups were let out to water twice daily and the walk to water was the only exercise they obtained. At these times, 8.30 a.m. and 4.30 p.m., oestrous observations were made. The animals were let out into a yard, 13 by 38 yd., from which they were driven into the farm yard to the water trough. While in the former yard, it was estimated that each animal walked 25 yards. While at the water trough the amount of walking was controlled as much as possible. It was estimated that each animal walked a total amount of 295 yards daily. The tendency for animals to run or to walk about was checked.

The Group C cattle went through the same daily routine with the exception that instead of returning to the stable after watering in the morning, as in the case of Groups A and B, the former group was allowed free exercise and abundant sunshine in a kraal, 50 by 68 feet, from 8.30 a.m. to 4.30 p.m. daily. It was calculated that, apart from the exercise in the kraal, Group C cattle walked 100 yards more each per day than those of Groups A and B. While it was impossible to estimate the amount of exercise obtained by the Group C cattle during a day, constant walking to and from the hay racks and being disturbed by one another, must have amounted to an appreciable amount daily. The exercise kraal had no shade or shelter apart from that afforded by a 6½ ft. stone wall on the east and a row of trees 30 yards distant on the west. The kraal was exposed to sunlight between 7.0. a.m. to 5.0 p.m. in summer and from 8.0 a.m. to 4.0 p.m. in winter.

During very wet weather Group C was stabled during the day.

It is, therefore, seen that while Groups A and B were kept in a dark stable and were exposed for a very short period, approximately ¾ hour daily, and had a very limited amount of exercise, Grop C could indulge in sunlight and exercise for eight hours daily.

The fact that none of the groups received green feed is stressed.

Further, general good management was given the cattle in all the groups. The cattle were handled with great care at all times. They were dipped in a 14-day strength arsenite of soda dip when deemed necessary, the essential precautions of cows in calf being taken in which case hand-dressing was, in preference, resorted to. It was found necessary to trim hoofs of the cattle at least once annually; this was particularly necessary in the case of Groups A and B.

The calves were allowed to suckle their mothers, care being taken not to allow the calves too much milk at first and then to thoroughly strip the udders of the cows by hand. During the first month from birth, the calves were allowed to suckle their mothers thrice daily, and thereafter twice daily. The calves were put in with their mothers after the latter had consumed their concentrate rations.

Teff hay was available to the calves during the day and when deemed necessary a small supplementary concentrate ration was fed to the calves. They were weaned at about six months old when they weighed about 400 lb.

Climatic Conditions.—The conditions at the Experiment Station may be considered to be representative of those of the eastern high-veld of the Transvaal. The altitude of Ermelo is 5,690 feet. The annual rainfall is in the vicinity of 27 inches, 90 per cent. of which falls during the summer months, October to March.

As a rule summer day-temperatures are high but the nights are cool, especially after thunder storms which are frequently experienced during the afternoons and evenings.

It may be said that the great majority of the days are bright and sunny. The winter nights are cold and frosty, but the day temperatures are mild to warm.

The following table of records supplied by the adjoining Government Forest Nursery, gives some indication of the rainfall and temperatures of the Experiment Station. The records for 1932 have been chosen as being fairly representa

Months (1932).	Rainfall.	Temperatures.	
		Maximum.	Minimum.
	Inches.	Range.	Range.
January	3·06	93·6–58 0	58 2–46·0
February	4·87	84 8–63 5	59·8–50·0
March	3·79	80 6–56 6	66·0–41·4
April	0·17	80 5–61·2	52 0–38·5
May	1·64	75 2–52 0	44·0–27·4
June	0 25	71·8–40 3	43 3–22·0
July	0 00	71·5–52 0	36 0–19·0
August	0 00	79·8–61·6	43·6–23·0
September	1 32	87 3–58·2	54·1–30·5
October	1·62	89 5–48·8	56·3–38·0
November	7 46	86 4–63·8	59 2–42·5
December	4 55	86 4–64·3	59·0–44·5

The total rainfall for the year 1932 was 28·73 in. It will be seen that temperatures fall rapidly from May and rise rapidly from September.

Observations.—Oestrous observations were made twice daily when the groups were let out to water at 8.30 a.m. and 4.30 p.m. Group C was let out first. The cattle were let out into the yard adjoining the stable and they were allowed to stand about in this yard for a few minutes before being brought into the larger yard to the water trough. The cattle were driven to the exercise yard in the morning and to their stable in the afternoon.

Groups A and B were let out together and the above procedure was carried out with the exception that these groups returned to their stable in the morning as well as in the afternoon.

The total time taken for the observations of the three groups was approximately 90 minutes a day.

At the commencement of the experiment, an ox was used as a " teaser " in testing for oestrus. However, it was soon found that the use of the ox was not necessary, as oestrus was easily observed or readily indicated. In most instances, individuals showing oestrus were anxious to mount others as soon as the former were loosened or as they entered the open yard. The mounting of the cow showing oestrus was usually vigorous and a clear mucous discharge from the vulva was seen. Frequently the cow stood near the cow it intended mounting, and the former was noticed to depress its back. Cows not showing oestrus willingly mounted cows showing oestrus, and the fact that the former are pregnant made no difference to their reactions. Cows showing oestrus readily stood to be mounted by other cows, the former appeared to be nervous and often bellowed.

In some cases a mucous discharge from the vagina was observed about 36 to 48 hours before oestrus was observed. This was usually seen in the stable when the cows were lying down.

Observations were not made to determine the duration of oestrus; however, the duration of oestrus did not appear to exceed 24 hours.

Haemorrhage, as indicated by a discharge of blood from the vagina, was observed to occur about 36-48 hours after oestrus was observed. Haemorrhage, however, did not consistently follow oestrus. On the other hand, haemorrhage was observed in some cases in non-pregnant individuals when oestrus was not shown immediately previous to haemorrhage. Heifer No. 3602 showed oestrus on 1.4.30, she showed haemorrhage on 24.4.30, and showed oestrus again on 11.5.30. It appeared that the heifer must have experienced a silent oestrus between 1.4.30 and 11.5.30.

A stable record sheet was kept on which to record all observations.

The serving of Groups A and C was commenced when the heifers were approximately 31 months old, while the heifers of Group B were given service 5 to 6 months later. The Sussex bull, No. 4242, previously referred to, was used for serving throughout the first three periods of the experiment. He was replaced by a younger bull, No. 6021 (Appendix I, Fig. 20) of the same breed at the commencement of the fourth period.

It was endeavoured to give service about 12 hours after the onset of oestrus. In some instances it was found that when oestrus was observed at 8.30 a.m., oestrus had passed off by 5 p.m. of the same day. This was no doubt due to the fact that oestrus had commenced some hours before it was observed. The time of the onset of oestrus could not be determined unless continuous observations were made.

During the first season of mating, services were given in a cattle crush, but subsequently the bull became too large and services had to be given in a yard. The bull was not held during service. In almost every instance, double services were given, the second following about 15 minutes after the first. It was found that, in a few cases, individuals would accept only one service, although in such cases they mounted the bull after the second service. Usually such individuals conceived from the one service. All females were put back into the stable after service.

All cows were mated again or given service about three months after calving.

Individuals showing a recurrence of oestrus were served at the first recurrence of oestrus. In the case of abortions service was delayed for one or two dioestrous cycles.

The cows were under close observation during pregnancy. When due to calve, they were kept in a loose box or semi-open shed during the nights. Only in the case of the first calf of No. 3594 was assistance given at parturition, and the assistance was considered slight.

All calves were weighed as soon as possible after birth; afterwards they were weighed at monthly intervals.

All the cows were weighed at monthly intervals, but the weighing was discontinued during advanced stages of pregnancy in order to eliminate undue excitement and the probabilities of abortion.

DISCUSSION.

It appears best to consider the data in three main sections which, under the headings of Breeding Tables A, B, C, and D, are termed First, Second, Third, and Fourth Periods. The First Period extends from the time of the commencement of the experiment up to the first calving; the Second Period, from the time of first calving up to the second calving, etc. Tables I to IV contain details of individual animals, but this information has been condensed in group form and it is presented in Table V, Breeding Table E.

Further tables have been compiled to permit more detailed analyses of such phases of the study as: Oestrus, gestation, etc.

The most important aspects of the study will be considered under the following sections:—

(1) Dioestrous cycles.

(2) Age and weight at successful service and at calving.

(3) Number of services required to establish pregnancy.

(4) Gestation periods.

(5) Birth weight of calves.

(1) *Dioestrous Cycles.*—Oestrous observations commenced when the heifers were approximately 15 months old. As the cattle were purchased from a private owner at that age, previous records of oestrus are not available.

Considerable variation exists with regard to the time of the first oestrus (Table I, Column 3). All the heifers exhibited their first oestrus before they were 24 months of age, although a period of slightly more than eight months elapsed before all the heifers had experienced their first oestrus. The following are the frequencies of the commencement of sexual activity during the months indicated:—

Group.	1929.	1930.								Total.
	June (10 (days).	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	
A............	—	1	—	—	5	1	—	1	1	9
B............	—	—	—	1	2	3	—	1	—	7
C............	—	1	2	1	1	—	—	2	1	8

There is, very apparently, no difference between the first occurrences of oestrus recorded for Groups A and B. In Group C, although three heifers showed oestrus during July and August, three individuals showed oestrus only in January and February (1930). No significance can be attached to the above variations as they may be ascribed to individual differences.

The dioestrous cycles detailed in Tables I to IV, have been analysed in Tables VI to X. When considering the total number of dioestrous cycles, it must be borne in mind that the numbers of cattle constituting the groups varied, and that alterations in numbers within groups occurred after the First Period. Also, it must be pointed out that as Group B was served 5-6 months later than Groups A and C, the first period of oestrous observations for Group B was correspondingly longer.

The dioestrous cycles of Groups A and C during the first period deserve attention (Table VI). The observations during the first period were recorded for nine heifers in Group A and 8 in Group C, the difference of the total dioestrous cycles is 41. The maximum dioestrous cycles in Group A for this period was 19 and in Group C 17 (Table I), hence assuming that an additional heifer in Group C would have recorded 19 dioestrous cycles, the remainder (41-19), 22 appears to be a significant difference. The cause of this difference can be seen by examining the distribution of the frequencies of the periodicity of oestrus in Table VI. In Group A, in seven instances dioestrous cycles ranged between 55 to 90 days, while in Group C, in twelve instances the dioestrous cycles ranged between 55-117 days, the longer periods being more frequent in the case of the latter group. Also, it will be seen from Table V that in the case of Group A in 76 per cent. of cases oestrus recurred after the normal interval of 18 and 23 days, while the equivalent figure for Group C is 70 per cent. Age, or difference in age, does not bear any influence upon this point, as the average ages of the cattle were approximately the same at the time of final or successful service. During this first period, it will be noticed (Table V) that in Group B in 80 per cent. of cases oestrus recurred after 18 to 23 days and although the range of dioestrous cycles was from 10-122 days, only seven dioestrous cycles, or 4·8 per cent., fell between 49 and 122 days.

During the Second and Third Periods (Tables VII, VIII, and IX), the length of time of oestrous observations was approximately equal for all groups, as all cows wer eserved about three months after parturition. During these periods, the total number of dioestrous cycles may be influenced by the length of time between calving and the first subsequent oestrus.

After the first calving, there was no significant difference between the total number of dioestrous cycles of the three groups (Table VII). The slightly larger total in the case of Group B was due to the larger number of shorter dioestrous cycles (Table VII) and the somewhat shorter interval (69·5 days) between calving and first oestrus as compared to Groups A (79·4 days) and C (89·5 days) (Table V).

After the second calving, the differences in the total dioestrous cycles are greater: Groups A: 15, B: 30, C: 6 (Table VIII). These differences resulted largely from the differences that existed between the periods between second calving and first subsequent oestrus, which were:—Groups A: 77·4 days, B: 56·3 days, C: 104·9 days (Table V). It will be noticed that, for this third period, the percentages of cases in which oestrus recurred after 18 to 23 days were: Group A: 57·1, B: 50·0 and C: 33·3. It is very apparent that Group B showed far greater ovarian activity during the third period than did either of the other two groups and especially Group C.

After the third calving, there is not that amount of significant difference in the total dioestrous cycles of the groups (Table IX) and there is also little difference in the period between parturition and first subsequent oestrus of Groups A (51·1 days) and B (54 days), but in the case of Group C the period is 83·2 days. It is seen that in the case of the fourth period the percentage of cases in which oestrus occurred after the normal interval of 18 to 23 days was considerably less than during the previous periods, viz., Group A: 30·8, Group B: 36·8 and Group C: 50·0.

From Tables VI to IX it has been ascertained that the mode of the dioestrous cycles of the groups for all four periods is twenty days. The range of the dioestrous cycles were from 10 to 123 days, but the highest percentage of dioestrous cycles fell between 18 and 23 days. It is, however, significant that there is a marked decrease in the percentage of cases in which the dioestrous cycle fell between the normal interval of 18 to 23 days as the experiment advanced.

It is seen from Table I that, during the long first period of oestrous observations, there were abnormally short and abnormally long dioestrous cycles during the first seven months. Therefore, it may be said that the heifers became more regular with respect to oestrus after they were approximately twenty-four months old.

(2) *Age and Weight.*—The details of ave and weight of the cattle are given in Tables I to IV; these details have been compiled for the groups and presented in Table V.

As previously stated, Group B was served 5-6 months later than the other two groups. The fact that certain individuals required a number of services before pregnancy was established resulted in a great diversity of age within groups. This is especially noticeable in Group A (Table V, column 5) in which the range of age at the end of the fourth period was from 77 to 91 months (and the average 82 months) at the fourth calving, whereas the corresponding figures for Groups B and C were, range 82-95 months, average 85 months, and range 77-85 months, average 80 months respectively.

All the cows were weighed monthly before the morning feeding and watering. Detailed weights (at the time of successful service) are given in Tables I to IV, and the averages for the groups are included in Table V.

It may be said that the condition of all groups has been very satisfactory throughout the period of the experiment. The cows gained weight during gestation and the great majority were in prime condition during the later part of pregnancy. They lost weight while suckling their calves, but gained in weight rapidly after the calves were weaned.

The birth-weights of the calves were recorded, and they were subsequently weighed at monthly intervals.

Calving data are given in detail in Table VI, and a summary for the groups is included in Table V.

During the use of the original bull, a slight increase is apparent in the average birth-weight of the calves of all groups as the age of the cows advanced, but here is a marked decrease in the weights of the calves served by the second bull used in the experiment (Table V, Column 7).

There is no significant difference between the birth-weights of the calves of Groups A and C, during the first three periods, but during the fourth period the calves of Group A were on an average 7·0 pounds heavier than Group C. The calves of Group B were considerably lighter during the first three periods than those of Groups A and C, but during the fourth period the same differences did not occur. It is interesting to note that the Group B cows were heavier or weighed more than the cows in the two other groups (Table V, column 3).

(3) *Number of Services required to Establish Pregnancy.*—The dates of all final or successful services are given in Table XI.

Table V, column 4, contains the frequencies of the services required to establish pregnancy. It is apparent that more services were required in Group A to establish pregnancy than was the case in Groups B and C. With regard to Group A. it cannot be said that the total number of services required to establish pregnancy increased with the ages of the cows. During the first period No. 3995 (Group A) required three services to establish pregnancy, during the second period only one, and during the third period four services. The services required by No. 3598 (Group A) were 2, 4, and 3 for the three periods.

In Group B, certain cows are of particular interest. In the first and second periods pregnancy was established in cows Nos. 3604, 3607, and 3608 by serving during one oestrus. However, in the third period No. 3604 required four services at different oestrous periods, Cow No. 3607 required ten services, and No. 3608 two services to establish pregnancy. During the first, second, and third periods cow No. 3602 required 1, 4, and 1 services respectively to establish pregnancy.

In Group C only three cows required re-serving during the three periods.

It is, therefore, apparent that Group C was outstanding with regard to the small number of services required to establish pregnancy. It is interesting to note that, during the fourth period in only one case did a cow require more than one service, viz. three, to establish pregnancy. This cow was No. 3614 in Group C. She required four services. The cow calved, 5.1.34, and, as she did not show oestrus within 209 days after parturition, she was examined and a persisting corpus luteum expressed from the ovary. She showed oestrus two days later and three further oestrous periods before becoming pregnant.

(4) *Gestation Periods.*—The gestation periods of each cow for the four periods are given in Tables I to IV, and the averages and ranges of gestation periods for the groups are given in Table V, column 6.

The frequencies of the gestation periods recorded are given in Table XII. It is apparent that there is no significant difference between the gestation periods of the three groups, neither is there any indication of differences between the duration of gestation of the first, second, third, and fourth periods.

With the exception of the gestation period of 264 days which was recorded for cow No. 3606 in Group B, the range of gestation for all groups was 271-289 days. Out of a total of 95 gestation periods, 81·05 per cent. fell between 276 and 286 days. Considering all groups the mode was 281 days (Table XII).

With the view of indicating the gestation periods of male and female offspring in each of the groups during the four periods, certain data have been extracted from Table XI and given in Table XIII. It appears from this table that there is no significant difference between the gestation periods of male and female calves; also there is no significant difference between the groups during the four successive periods, nor does any particular group show significant variation during the four successive periods.

The mode gestation period was previously stated to have been 281 days. From Table XIII it is computed that the average gestation period was 279·6 days.

With the exception of the calf of No. 3606 which was born during the second period, the gestation period of which was 264 days, all calves were exceedingly healthy when born and they made rapid progress in growth. The calf of No. 3606 was born with congenital ichthyosis and it died when 14 days old.

CONCLUSIONS.

(1) The effects of a dry ration, high condition, the absence of sunlight, and exercise upon the sexual activity and reproduction of beef females have been studied. The results obtained during six years of observations are reported upon; the period includes four calvings.

(2) When a dry ration consisting of maize, wheaten bran, and teff hay is fed for nine months and silage is added to the ration during the remaining three months of the year, very satisfactory results may be expected.

The ration induces satisfactory growth of young heifers and maintains mature animals in good condition.

Sexual maturity is reached before the age of 24 months, and sexual activity and reproduction are in no way impaired.

(3) High condition causes no ill effects either upon general health or the reproductive processes.

(4) The restriction of sunlight and exercise in no way detrimentally affects the health, growth, and vigour of heifers and cows being fed dry rations. The onset of maturity is not delayed. Up to the age of 32 months or prior to being bred, a large number of dioestrous cycles are seen to have been experienced by the heifers receiving restricted sunlight and exercise. The animals receiving an abundance of sunlight and exercise, experienced a larger number of abnormally long dioestrous cycles. The mode of the dioestrous cycles is 20 days, and although cycles as short as 10 days and as long as 123 days are experienced, about 75 per cent. of dioestrous cycles fall between 18 and 23 days. It appears that as the ages of the animals advanced, under the special environmental conditions enforced, the percentage of dioestrous cycles between 18-23 days decreased.

(5) A restriction of sunlight or exercise appears to shorten rather than to lengthen the period between calving and the first subsequent oestrus. Oestrus is observed to occur as soon as 15 and 21 days after calving. Although, in the majority of cases, the period of inactivity is in the vicinity of 60 days, many cases of over 100 days occur. and cases even over 200 days may be encountered. There appears to be a tendency for the period of inactivity to shorten as the ages of the cows advance between 3 and 6 years.

(6) Unrestricted sunlight and exercise result, in fewer services being required to establish pregnancy. Failure to conceive after the first and second service cannot be considered exceptional and this appears to be the case especially in young animals. The number of services required to establish fertility decreases as the ages of cows advance.

(7) The length of the gestation period is unaffected by limiting sunlight and exercise. Out of a total of 95 gestation periods, the mode is 281 days, the average 279·6 days, and 81 per cent. of the periods fall between 276 and 286 days. There is no tendency for the gestation periods to alter with advancing age. There is no difference between the gestation periods of males or females.

(8) Unrestricted sunlight and exercise do not reflect any advantage upon the weight of calves produced. Few of the calves obtained are seen to have weighed under 60 pounds at birth, while weights up to 98 and 99 pounds were recorded. It is seen that the change of the bull greatly influenced the birthweight of the calves.

(9) High conditioned heifers, under conditions of restricted sunlight or exercise, show no tendency towards abnormal sexual activity when breeding is delayed until the heifers are 35 months of age. The reproductive functions of the animals are unaffected when breeding is delayed for this period. Cows which maintain a higher condition throughout the periods of gestation, lactation, and rest are likely to produce calves which are small and light in weight.

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APPENDIX I.

I. FEMALES UPON WHICH OBSERVATIONS WERE MADE.

Group A.

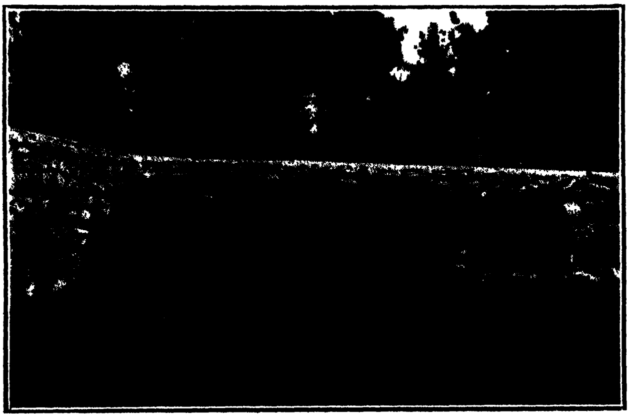

Fig. 1.—As heifers 28 months old and 13 months in the experiment (July, 1930).

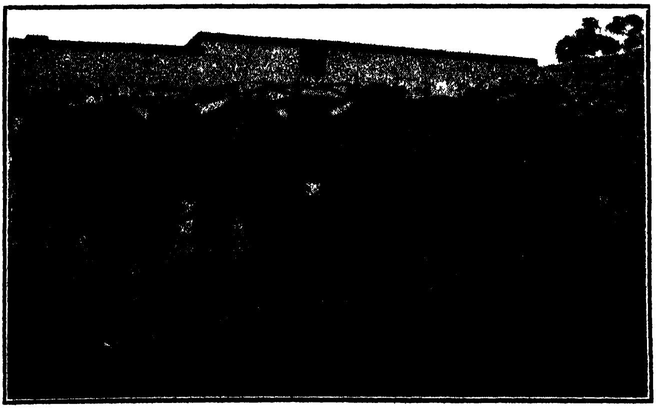

Fig. 2.—38 months old and 6-7 months pregnant (May, 1931).

GROUP A.

Fig. 3.—66 months old and 7-8 months pregnant (September, 1933).

Fig. 4.—84 months old, after fourth calving (March, 1935).

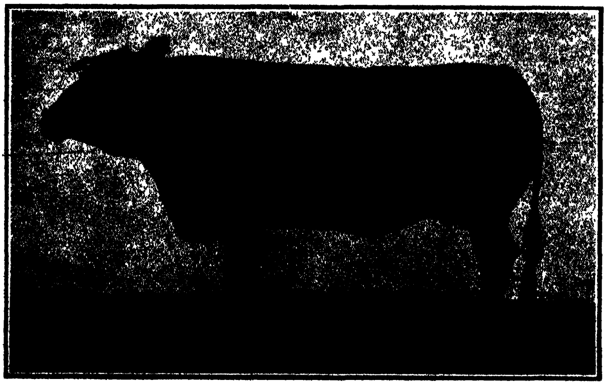

Fig. 5.—No. 3595, 2 months pregnant (October, 1934).

GROUP A.

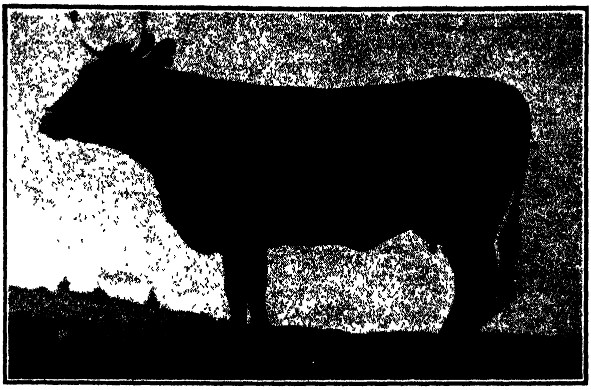

Fig. 6.—No. 3598, 8½ months pregnant (October, 1934).

GROUP B.

Fig. 7.—As heifers 28 months old and 13 months in the experiment (July, 1930).

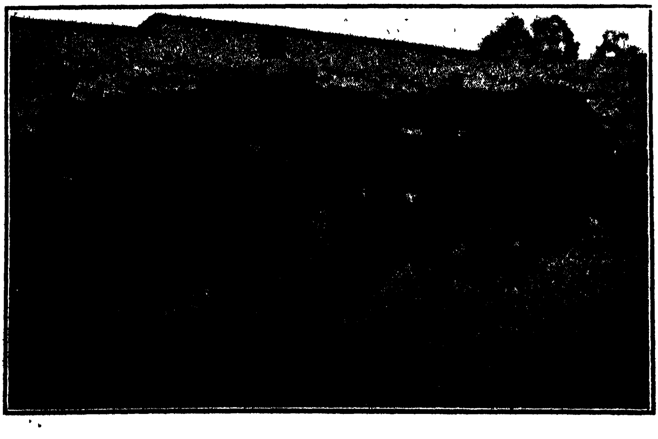

Fig. 8.—38 months old and 1 month pregnant (May, 1931)

GROUP B.

Fig. 9.—66 months old and 4 months pregnant (September, 1933).

Fig. 10.—84 months old, before fourth calving (March, 1935).

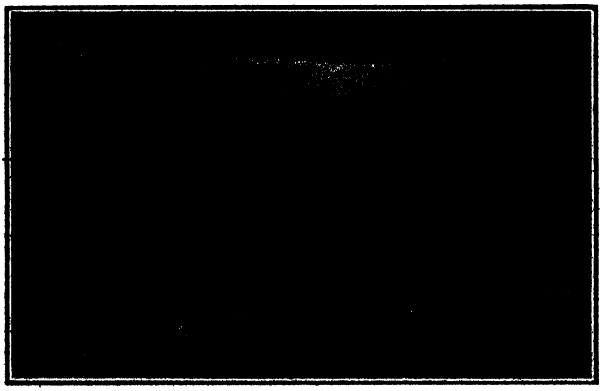

Fig. 11.—No. 3606, 4 months pregnant (October, 1934).

GROUP B.

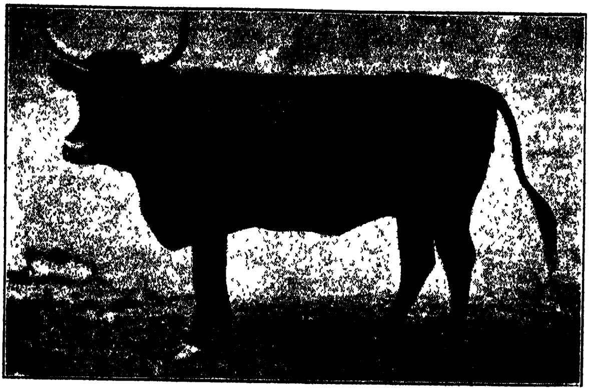

Fig. 12.—No. 3609, 4 months pregnant (Ocotober, 1934).

GROUP C.

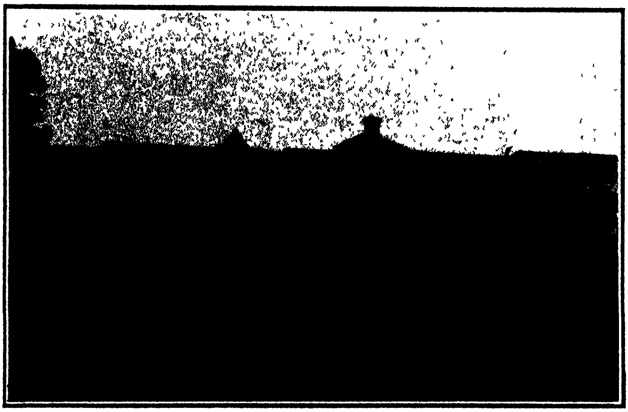

Fig. 13.—As heifers 28 months old and 13 months in the experiment (July, 1930).

Fig. 14.—38 months old and 6-7 months pregnant (May, 1931).

GROUP C.

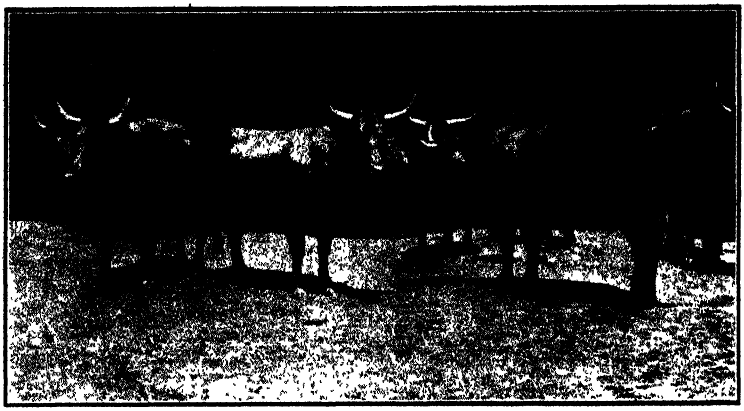

Fig. 15.—66 months old and 7-8 months pregnant (September, 1933).

Fig. 16.—84 months old after fourth calving (March, 1935).

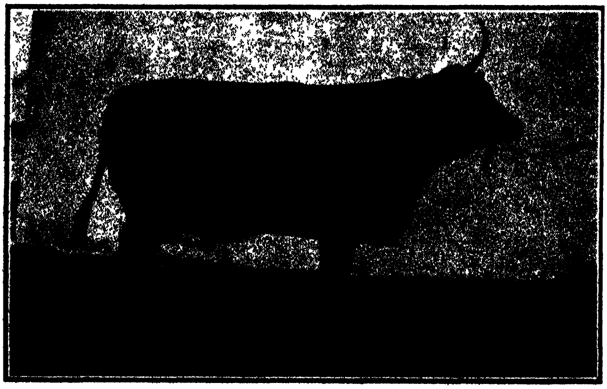

Fig. 17.—No. 3611, 5 months pregnant (October, 1934).

GROUP C.

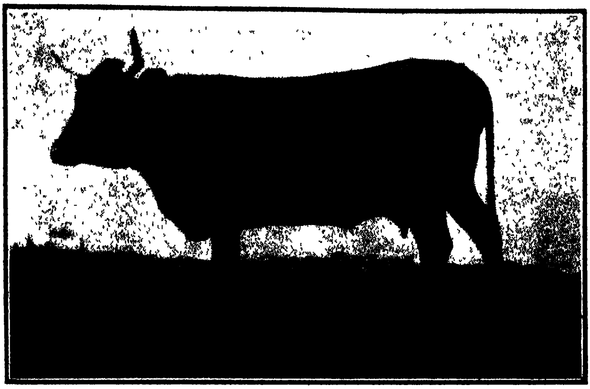

Fig. 18.—No. 3620, 8 months pregnant (October, 1934).

II. PURE BRED SUSSEX BULLS USED IN THE EXPERIMENT.

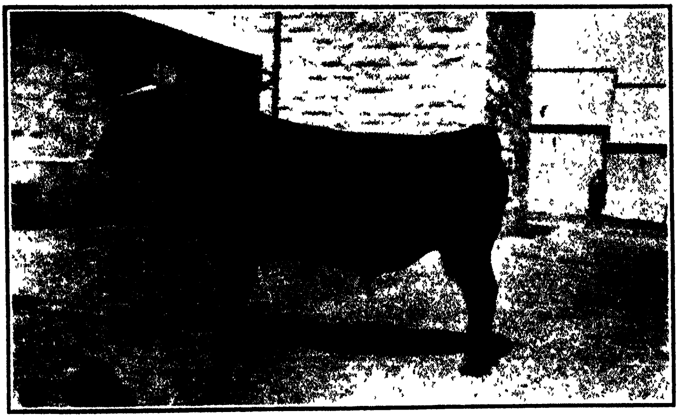

Fig. 19.—No. 4242: Used from 17.10.30-21.12.33.

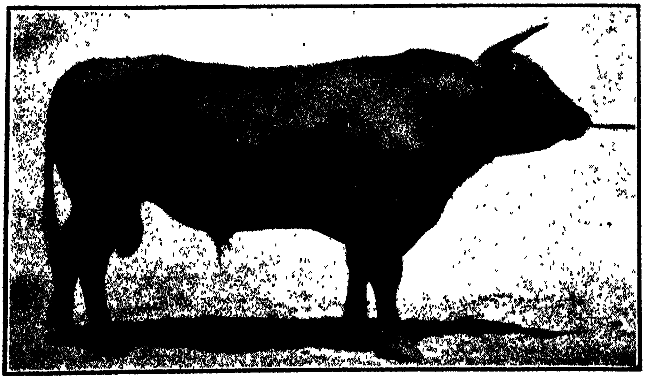

Fig. 20.—No. 6021: Used from 22.12.33- 5.10.34.

III. CALVES OUT OF THE EXPERIMENTAL COWS.

(a) GROUP A CALVES.

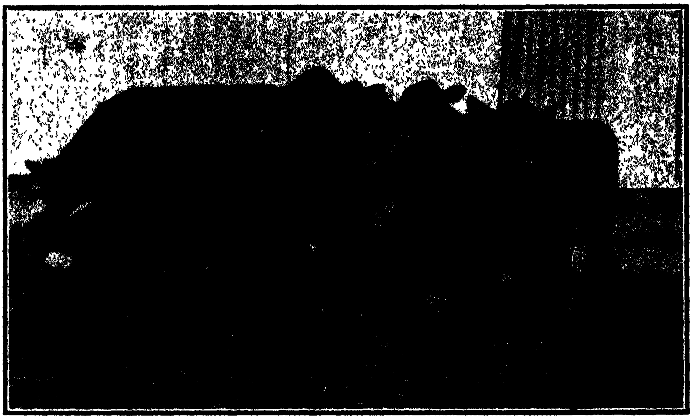

Fig. 21.—1st Calves, 3-4 months old.

Fig. 22. –1st Calves, 5-6 months old.

Fig. 23.—1st Calves, 8-9 months old.

III. CALVES OUT OF THE EXPERIMENTAL COWS.

(*a*) GROUP A CALVES.

Fig. 24.—2nd Calves 7 months old and younger.

Fig. 25.—2nd Calves approximately 12 months old.

Fig. 26.—3rd Calves, 9 months old.

III. CALVES OUT OF THE EXPERIMENTAL COWS.

(a) Group A Calves.

Fig. 27.—3rd Calves 15-16 months old.

Fig. 28.—4th Calves, 3-4 months old.

Fig. 29.—4th Calves, 8-9 months old.

(b) GROUP B CALVES.

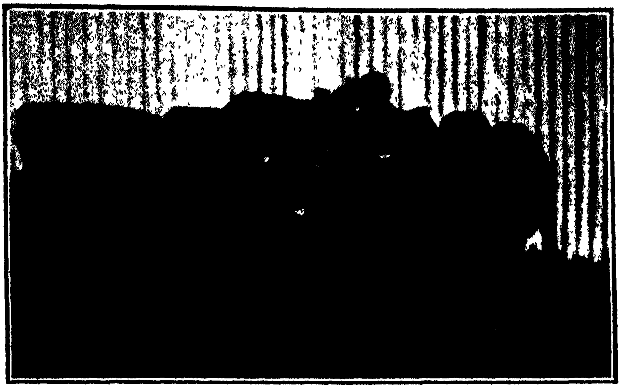

Fig. 30.—1st Calves, 1-6 months old.

Fig. 31.—1st Calves, 9-10 months old.

Fig. 32.—1st Calves, 17-18 months old.

(b) GROUP B CALVES.

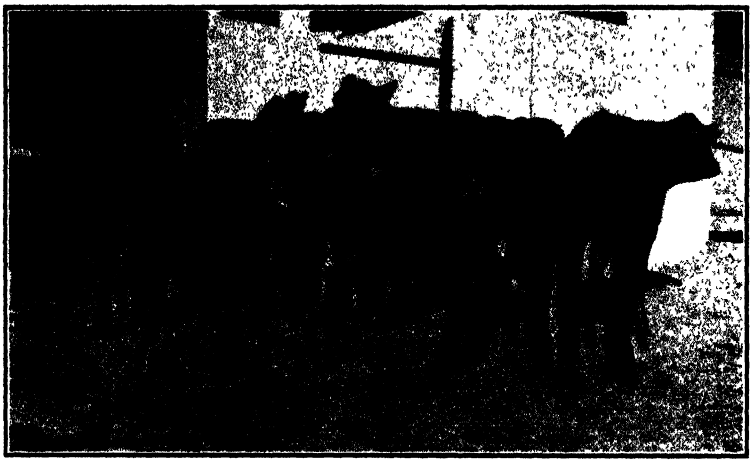

Fig. 33.—2nd Calves, 3-4 months old.

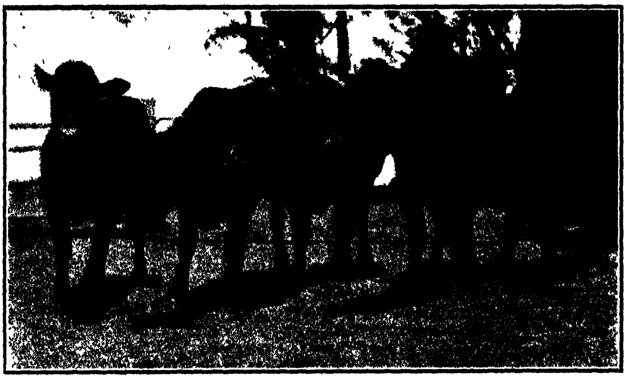

Fig. 34.—2nd Calves, 24-26 months old.

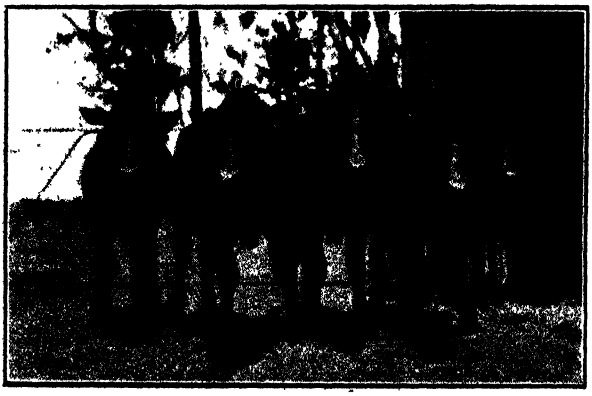

Fig. 35.—3rd Calves, 12-13 months old.

(*b*) GROUP B CALVES.

Fig. 36.—4th Calves, 5-6 months old.

(*c*) GROUP C CALVES.

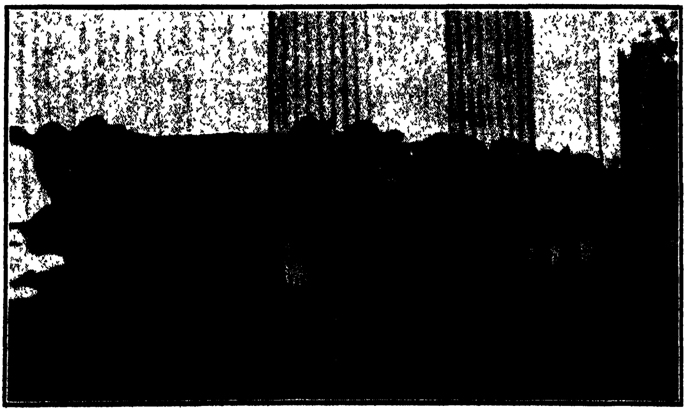

Fig. 37.—1st Calves, 3-4 months old.

(c) GROUP C CALVES.

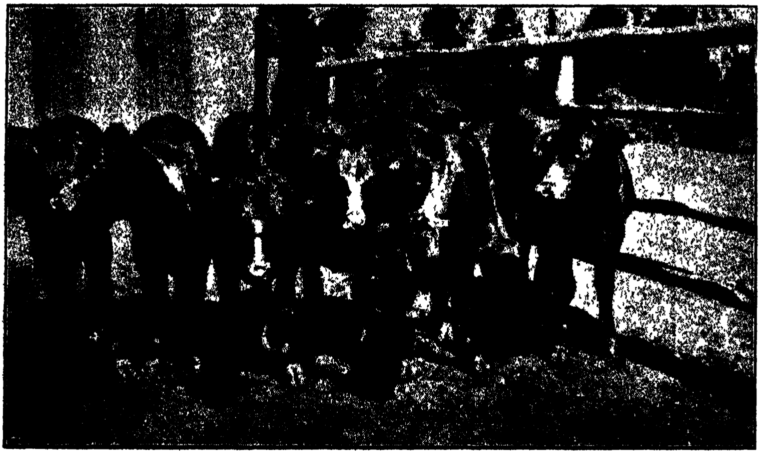

Fig. 38.—1st Calves, 5-6 months old.

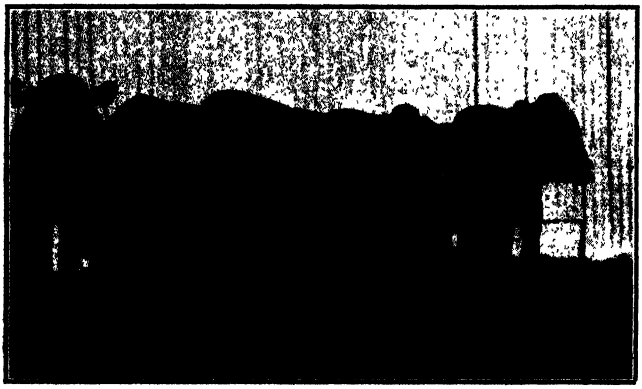

Fig. 39.—1st Calves, 8-9 months old.

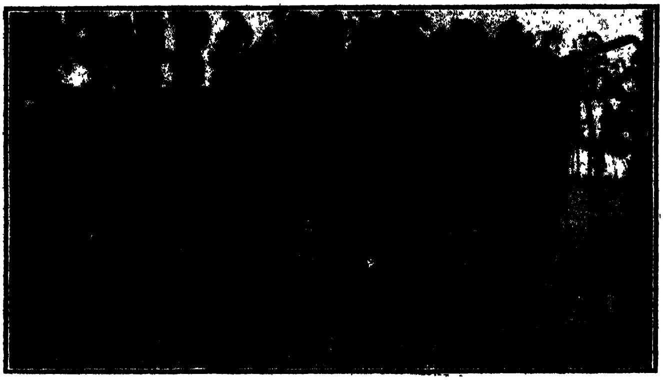

Fig. 40.—2nd Calves, 7 months and younger.

(c) Group C Calves.

Fig. 41.—2nd Calves, 9-12 months old.

Fig. 42.—3rd Calves, 15-16 months old.

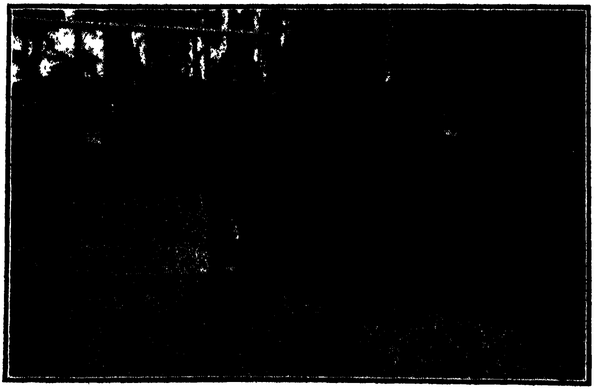

Fig. 43.—4th Calves, 3-4 months old.

(*c*) Group C Calves.

Fig. 44.—4th Calves, 8-9 months old.

APPENDIX II.

The following Tables, I-XIII, show in summarized form the data accumulated during the course of the observations up to the end of the fourth gestation period; that is from June, 1929, to July, 1935:—

TABLE 1.

Breeding Table A : First Period, 1929-1931.

Group and D.O.B. No.	Approximate Age at which Oestrous Observations began (20.6.29).	Date on which First Oestrus was Observed.	*Observation Periods*—Groups A and C: June, 1929–December, 1930. Group B: June, 1929–April, 1931. The Periodicity of Oestrus in Days.	Total Number of Di-oestrus Periods.	Approximate Age at Final Service.	Weight at Final Service.	Number of Services required to Establish Pregnancy.	Gestation Period.	Sex of Calf.	Birth-Weight of Calf.
GROUP A.	Months.				Months.	Lb.		Days.		Lb.
3591.......	15	3.10.29	40 18 18 21 20 19 20 21 21 21 20 21 20 20 21 21 22 21 23	19	32	937	2 (*a*)	—	—	—
5332.......	15	27. 2.30	19 22 19 20 20 21 20 21 21 20 19 21	12	31 : 37 (*b*)	930	1 : 2 (*b*)	277	Male	82·0
3533.......	15	5.10.29	25 21 38 18 19 38 39 39 19 20 19 20 22 21 19	15	31	882	1	277	Female	60·0
3594.......	15	30. 7.29	55 23 20 17 26 10 28 21 38 20 20 21 20 20 20 19 21 20 40	19	31	989	1	285	Male	86·5
3595.......	15	16.10.29	63 15 61 19 37 19 20 20 19 19 21 18 18 39 17 18	16	33	1,108	3	275	Male	75·5
3597.......	15	25. 1.30	38 14 24 22 19 19 20 20 20 20 20 19 21	13	31	916	1	280	Male	75·0
3598.......	15	24.11.29	16 16 18 28 21 24 22 23 23 20 24 22 23 21 21 21 23	17	32	907	2	281	Female	73·5
3599.......	15	16.10.29	14 22 50 22 84 18 21 20 20 22 38 22 19 21	14	32	917	2	281	Female	72·0
3600.......	15	17.10.29	19 21 55 90 20 20 20 19 23 22 22 24 21 23	14	32	1,034	2	280	Female	90·5
GROUP B.										
3601.......	15	26.11.29	122 19 19 20 20 21 20 21 20 19 19 22 20 21 19 21 20 19 19 18	20	36	901	1	277	Female	66·0
3602.......	15	26.11.29	14 18 18 20 38 21 19 18 19 19 20 19 21 19 20 20 24 20 19 20 20 22 21 19 18	25	37	1,109	1	272	—	—
3604.......	15	30.10.29	22 27 10 28 21 21 20 21 22 21 21 21 21 21 21 19 24 18 21 21 20 22 20 20 20 22	26	37	1,111	1	281	Female	51·0
3605.......	15	24.11.29	24 61 40 43 21 19 21 23 21 20 21 19 24 17 17 23 21 21 20 20	20	36	1,132	1	278	Female	61·0
3606.......	15	30.10.29	59 72 24 37 40 19 20 20 22 19 23 22 20 20 20 20 20 21 20 20	20	37	1,092	1	287	Male	86·0
3607.......	15	18. 1.30	21 23 28 20 79 18 19 49 20 19 21 20 20 20 20	15	36	1,025	1	287	Female	80·0
3608.......	15	15. 9.29	43 43 39 54 20 22 21 22 22 23 23 22 19 20 24 23 23 22 22 24 19	21	37	1,142	1	279	Male	70·0
GROUP C.										
3611.......	15	13. 1.30	72 20 22 18 20 21 21 20 21 23 19 21	12	31	1,057	2	279	Male	65·5
3612.......	15	30. 7.29	117 18 63 16 40 22 23 22 23 23 20 46 27	13	32	1,009	1	271	Male	65·0
3613.......	15	30. 9.29	105 44 20 42 21 19 20 20 21 82	10	31	1,092	1	288	Male	96·0
3616.......	15	5. 8.29	40 16 22 51 63 20 21 21 21 21 20 21 21 22 22 22 21	17	31	1,181	1	286	Female	77·5
3617.......	15	9. 1.30	81 22 37 21 20 21 20 21 20 20	10	31	842	1	289	Female	75·0
3618.......	15	1.10.29	77 23 105 22 20 22 21 21 20 22 20 23	12	31	1,007	1	282	Male	87·5
3619.......	15	13. 2.30	20 36 18 18 36 18 55 18 54	9	32	842	1	277	Male	69·0
3620.......	15	7. 8.29	55 77 23 48 20 16 24 19 20 38 21 19 20 20 20	15	31	937	1	282	Female	75·0

NOTE.—(*a*) No. 3591 was killed *in extremis* and was found to be non-pregnant.
(*b*) No. 3592 aborted after 4½ months pregnancy, conceived again after two services. Inverted uterus after calf-birth.
(*c*) No. 3602 aborted 272 days after conception, cause unknown.

TABLE II.

Breeding Table B: Second Period, 1931-1932.

Group and D.O.B. No.	Approximate Age at Second Calving.	Period between Calving and First Oestrus.	The Periodicity of Oestrus (days).					Total Number of Di-oestrus Periods.	Period between Calving and last Oestrus or next Service.	Approximate Age at Final Service.	Weight at Final Service.	Number of Services to Establish Pregnancy.	Length of Gestation Period.	Sex of Calf.	Birth-weight of Calf.
GROUP A.	Months.	Days.							Days.	Months.	Lb.		Days.		Lb.
3593	40	61	44	19	123	20		4	267 (c)	54	1,002	3	281	Male	82·0
3594	40	104						—	104	44	1,125	1	279	Male	77·0
3595	42	66						—	66	44	1,340	1	284	Female	67·0
3596	—	— (a)	21					1	-	46	960	1	277	Male	73·5
3597	40	85	33	19				2	137	45	1,053	1	272	Female	68·0
3598	41	92	80	42	96			3	310	51	1,020	4	284	Female	77·0
3599	41	81						—	81	44	1,074	1	282	Male	80·0
3600	41	67	50					1	117	45	1,210	1	286	Female	94·0
GROUP B.															
3601	45	57	20	20				2	97	49	1,079	1	282	Male	79·0
3602	46	Aborted 13.1.32 (b)	21	21	21	44	79	5	—	53	1,171	4	284	Female	56·5
3603	—	— (a)	21	21	23	20		4	—	48	1,175	1	281	Male	79·5
3604	46	51	23					1	74	49	1,325	1	281	Female	60·0
3605	45	46	43					1	89	48	1,290	1	286	Female	75·0
3606	46	73						—	73	49	1,075	1	264	Female	52·0
3607	45	91						—	91	48	1,150	1	285	Female	77·0
3608	46	99						—	99	49	1,177	1	279	Female	77·5
3609	—	— (a)						—	—	48	1,065	1	282	Female	83·5
GROUP C.															
3611	40	73	66	45				2	184	46	1,015	1	281	Male	78·0
3612	41	100						—	100	44	1,120	1	274	Female	67·0
3613	40	124						—	124	44	1,225	1	284	Female	84·0
3614	—	— (a)						—	—	45	980	1	282	Female	71·0
3616	40	73	22	20	57			3	172	46	1,208	2	281	Female	80·0
3617	40	127						—	127	44	963	1	284	Male	90·0
3618	40	72	22	22				2	116	44	1,095	1	286	Male	94·0
3619	41	63	21	60				2	144	45	1,018	1	277	Female	66·0
3620	40	84	21	22				2	127	44	1,034	1	280	Male	69·0

NOTE.—(a) Nos. 3596, 3603, 3609, and 3614 were drafted back into the experiment on 11.12.31.
(b) No. 3602 aborted and was served about 3 months after the abortion.
(c) No. 3593 conceived to this service, but aborted after 4½ months and was served again 19 days after the abortion, to which service she conceived and eventually calved.

TABLE III.

Breeding Table C: Third Period, 1932-1933.

Group and D.O.B. No.	Approximate Age at Second Calving.	Period between Calving and First Oestrus.	The Periodicity of Oestrus (days).	Total Number of Di-oestrus Periods.	Period between Calving and last Oestrus or next Service.	Approximate Age at Final Service.	Weight at Final Period. Service.	Number of Services to Establish Pregnancy.	Length of Gestation Period.	Sex of Calf.	Birth-weight of Calf.
GROUP A.	Months.	Days.			Days.	Months.	Lb.		Days.		Lb.
3593	63	58		—	58	65	1,105	1	281	Female	69·0
3594	53	56	22 21	2	99	56	952	1	282	Female	74·5
3595	53	61	21 19 39 40 78 22 54	7	334	64	1,353	4	278	Male	71·0
3596	55	85		—	85	58	899	1	275	Female	64·0
3597	54	84	19	1	103	57	958	1	281	Male	81·0
3598	60	70	22 112 20 67	4	224	70	978	3	276	Female	53·0
3599	53	98	64	1	162	58	1,061	1	283	Male	87·0
3600	54	107		—	107	58	1,062	1	285	Male	99·0
GROUP B.											
3601	58	39	39 44	2	122	62	1,000	1	282	Female	78·0
3602	63	102		—	102	66	1,114	1	286	Male	69·5
3603	57	128		—	128	61	1,204	1	281	Male	68·0
3604	58	38	80 23 28 21	4	190	64	1,375	4	281	Female	53·0
3605	57	37	21 67	2	125	61	1,274	1	276	Male	76·0
3606	58	36	42 21 21	3	120	62	1,272	1	276	Female	75·0
3607	57	29	41 51 50 21 62 33 22 21 19 88 39	11	319	72	—	10	280	Male	69·0
3608	58	29	52 24 21 Aborted 22.8.33 44 21	5	266	67	—	1, aborted 2	279	Female	70·0
3609	57	69	21 21 22	3	133	61	1,170	2	280	Male	98·0
GROUP C.											
3611	55	126	22 20	2	168	61	1,105	1	279	Female	75·0
3612	53	70	27	1	97	56	1·022	1	276	Male	75·5
3613	53	115		—	115	57	1,107	1	277	Male	82·0
3614	54	164		—	164	59	892	1	284	Male	75·0
3616	55	77		—	77	58	1,127	1	284	Female	86·0
3617	53	117	77 42	2	236	61	850	3	279	Female	73·0
3618	53	57	43	1	100	56	1,011	1	286	Female	87·0
3619	54	90		—	99	57	983	1	274	Female	71·0
3620	53	119		—	119	57	925	1	286	Male	76·0

TABLE IV.

Breeding Table D: Fourth Period, 1933-1934.

Group and D.O.B. No.	Approximate Age at Third Calving.	Period between Calving and First Oestrus.	The Periodicity of Oestrus (days).				Total Number of Di-oestrus Periods.	Period between Calving and last Oestrus or next Service.	Approximate Age at Final Service.	Weight at Final Service.	Number of Services to Establish Pregnancy.	Length of Gestation Period.	Sex of Calf.	Birth-weight of Calf.
GROUP A.	Months.	Days.						Days.	Months.	Lb.		Days.		Lb.
3593	74	44	21	20			2	85	77	816	1	285	Female	59·0
3594	65	21	41	21	20		3	103	68	960	1	283	Female	77·5
3595	73	41	21	21			2	83	76	1,202	1	273	Male	65·0
3596	67	67	20				1	87	70	892	1	272	Female	61·0
3597	66	55	20	21			2	96	69	985	1	278	Male	75·0
3598	79	79					—	79	82	1,000	1	276	Female	53·0
3599	67	62	42				1	104	70	1,083	1	279	Male	78·0
3600	67	40	24	44			2	108	71	1,127	1	282	Female	54·5
GROUP B.														
3601	71	39	21	20	21	20	4	121	75	917	1	282	Male	51·0
3602	75	77	19				1	96	78	997	1	—	—	—
3603	70	27	44	22			2	93	73	1,300	1	272	Female	57·0
3604	73	36	19	41			2	96	76	1,317	1	273	Male	59·0
3605	70	33	22	21	24		3	100	73	1,214	1	277	Male	53·0
3606	71	120					—	120	75	1,247	1	276	Male	66·0
3607	81	52	20	40	40		3	152	86	1,263	—	—	—	—
3608	76	49	19	24			2	92	79	1,122	1	279	Female	70·0
3609	70	52	24	22			2	98	73	1,094	1	276	Male	79·0
GROUP C.														
3611	70	64	21				1	85	73	1,148	1	278	Female	60·0
3612	65	47	23	27			2	97	68	1,075	1	269	Female	51·0
3613	66	186					—	186	72	1,130	1	269	Female	47·5
3614	68	211	20	20	82		3	333	79	1,002	4	—	—	—
3616	67	49	22	22			2	93	70	1,065	1	276	Male	77·0
3617	70	60	51				1	111	74	864	1	278	Female	44·0
3618	65	37	45	69			2	151	70	1,034	1	Aborted 28.	11.34. Died	4.12.34.
3619	66	60	41				1	101	69	998	1	272	Male	57·0
3620	66	35	23	41			2	99	69	891	1	280	Male	72·5

TABLE V.

Breeding Table E.

	Di-oestrus Periods.			Approximate Age at Final or Successful Service.		Weight at Final or Successful Service.		Number of Services required to Establish Pregnancy.											
								Frequencies.											
	Total.	Range.	Mode.	Range.	Average.	Range.	Average.	1	2	3	4	5	6	7	8	9	10	11	12
GROUP A.		Days.	Days.	Months.	Months.	Lb.	Lb.												
1st Period.......	139	10– 90	20	31–33	32	907–1.108	958	4	3	1	—	—	—	—	—	—	—	—	—
2nd Period.......	11	19–123	19	44–54	47	960–1.340	1.098	6	—	1	1	—	—	—	—	—	—	—	—
3rd Period.......	15	19–112	22	56–70	61	952–1,353	1,056	6	—	1	1	—	—	—	—	—	—	—	—
4th Period.......	13	20– 44	21	68–82	73	816–1.202	1.008	8	—	—	—	—	—	—	—	—	—	—	—
GROUP B.																			
1st Period.......	147	10–122	20	36–37	35	901–1,142	1.073	7	—	—	—	—	—	—	—	—	—	—	—
2nd Period.......	13	20– 79	21	48–53	49	1.065–1,325	1.167	8	—	—	1	—	—	—	—	—	—	—	—
3rd Period.......	30	19– 88	21	61–72	64	1.000–1,375	1,201	6	2	—	1	—	—	—	—	—	—	1	—
4th Period.......	19	19– 44	—(*a*)	73–86	76	917–1,317	1.162	8	—	—	—	—	—	—	—	—	—	—	—
GROUP C.																			
1st Period.......	98	16–117	20	31–32	31	842–1,181	995	7	1	—	—	—	—	—	—	—	—	—	—
2 d Period.......	11	20– 66	22	44–46	45	980–1,225	1,073	8	1	—	—	—	—	—	—	—	—	—	—
3rd Period.......	6	20– 77	—(*a*)	56–61	58	850–1.127	1,002	8	—	1	—	—	—	—	—	—	—	—	—
4th Period.......	14	20– 82	—(*a*)	68–79	72	864–1,148	1.023	8	—	1	—	—	—	—	—	—	—	—	—

	Approximate Age at Calving.		Length of Gestation Period.		Birth-weight of Calves.		Sex of Calves.		Period between Calving and First Oestrus.		Period between. Calving and last Oestrus or next Service.	
	Range.	Average.	Range.	Average.	Range.	Average.	Male.	Female.	Range.	Average.	Range.	Average.
GROUP A.	Months.	Months.	Days.	Days.	Lb.	Lb.			Days.	Days.	Days.	Days.
1st Period.........	40–42	41	275–285	279·5	60–90	76·9	4	4	61–104	79·4	66–267	153·7
2nd Period.........	53–63	56	272–286	280·6	67–94	77·3	4	4	56–107	77·4	58–334	146·5
3rd Period.........	65–79	70	275–285	280·7	64–99	77·9	4	3	21– 79	51·1	79–108	93·1
4th Period.........	77–91	82	272–285	278·5	53–78	65·4	3	5	32– 87	60·3	79–155	103·2
GROUP B.												
1st Period.........	45–46	46	272–287	280·1	51–86	69·0	2	4	46– 99	69·5	73– 93	87·2
2nd Period.........	58–63	58	264–286	280·4	52–83	71·7	2	7	39–128	56·3	102–266	148·2
3rd Period.........	70–81	73	276–286	280·1	53–98	73·4	5	4	27–120	54·0	92–152	107·6
4th Period.........	82–95	85	272–282	276·1	51–79	62·1	5	2	—	—	—	—
GROUP C.												
1st Period.........	40–41	40	271–289	281·8	65–96	76·3	5	3	63–127	89·5	100–184	136·8
2nd Period.........	53–55	54	274–286	281·0	66–94	77·7	4	5	57–164	104·9	77–236	130·6
3rd Period.........	65–70	67	274–286	280·5	71–87	77·8	4	5	35–211	83·2	85–333	139·6
4th Period.........	77–85	80	269–280	274·6	44–79	58·4	3	4	15– 95	53·2	73–171	103·2

NOTE.—(*a*) No mode.

TABLE VI.

Frequencies of the Periodicity of Oestrus: First Period, 1929-1931.

Periodicity of oestrus in days:—

Number of Individuals.	10	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	33	36	37	38	39	40	42	43
Group A: 9..............	1	2	1	2	2	8	19	31	27	12	8	4	1	1	—	2	—	—	1	5	3	2	—	—
Group B: 7..............	1	1	—	—	2	7	23	38	28	14	8	7	—	—	1	2	—	—	1	1	1	2	—	3
Group C: 8..............	—	—	—	3	—	6	4	23	19	11	7	1	—	—	1	—	—	2	1	1	—	2	1	—
TOTAL: 24........	2	3	1	5	4	21	46	92	74	37	23	12	1	1	2	4	—	2	3	7	4	6	1	3

Number of Individuals.	44	46	48	49	51	54	55	59	60	61	63	72	75	77	79	81	82	84	90	105	117	122	Totals.
Group A: 9............	—	—	—	—	—	—	2	—	1	1	1	—	—	—	—	—	—	1	1	—	—	—	139
Group B: 7............	—	—	—	1	—	1	—	1	—	1	—	1	—	—	1	—	—	—	—	—	—	1	147
Group C: 8............	1	1	1	—	1	1	2	—	—	—	2	1	—	2	—	1	1	—	—	2	1	—	98
TOTAL: 24.......	1	1	1	1	1	2	4	1	1	2	3	2	—	2	1	1	1	1	1	2	1	1	384

TABLE VII.
Second Period, 1931-1932.

Periodicity of oestrus in days:—

Number of Individuals.	19	20	21	22	23	33	42	43	44	45	50	57	60	66	79	80	96	123	Totals.
Group A: 8..............	2	1	1	—	—	1	1	—	1	—	1	—	—	—	—	1	1	1	11
Group B: 9..............	—	3	5	—	2	—	—	1	1	—	—	—	—	—	1	—	—	—	13
Group C: 9..............	—	1	2	4	—	—	—	—	—	1	—	1	1	1	—	—	—	—	11
TOTALS: 26.........	2	5	8	4	2	1	1	1	2	1	1	1	1	1	1	1	1	1	35

TABLE VIII.
Third Period, 1932-1933.

Periodicity of oestrus in days:—

Number of Individuals.	19	20	21	22	23	24	25	26	27	28	33	39	40	41	42	43	44	50	51	52	54	62	64	67	77	78	80	88	112	Totals.
Group A: 8............	2	1	2	3	—	—	—	—	—	—	—	1	1	—	—	—	—	—	—	—	1	—	1	1	—	1	—	—	1	15
Group B: 9............	1	—	10	2	1	1	—	—	—	1	1	2	—	1	1	—	2	1	1	1	—	1	—	1	—	—	1	1	—	30
Group C: 9............	—	1	—	1	—	—	—	—	1	—	—	—	—	—	1	1	—	—	—	—	—	—	—	—	1	—	—	—	—	6
TOTALS: 26......	3	2	12	6	1	1	—	—	1	1	1	3	1	1	2	1	2	1	1	1	1	1	1	2	1	1	1	1	1	51

TABLE IX.
Fourth Period, 1933-1934.

Periodicity of oestrus in days:—

Number of Individuals.	19	20	21	22	23	24	27	40	41	42	44	45	51	69	82	Totals.
Group A: 8................	—	4	5	—	—	1	—	—	1	1	1	—	—	—	—	13
Group B: 9................	3	3	3	3	—	3	—	2	1	—	1	—	—	—	—	19
Group C: 9................	—	2	1	2	2	—	1	—	2	—	—	1	1	1	1	14
TOTALS: 26...........	3	9	9	5	2	4	1	2	4	1	2	1	1	1	1	46

TABLE X.

The Dioestrous Periods, 1929-1934.

Group.	First Period, 1929–1931.			Second Period, 1931–1932.		
	Dioestrous Periods.		Percentage of Cases in which Oestrus Recurred after the Normal Interval of 18–23 Days.	Dioestrous Periods.		Percentage of Cases in which Oestrus Recurred after the Normal Interval of 18–23 Days.
	Range.	Mode.		Range.	Mode.	
	Days.	Days.		Days.	Days.	
A	10– 90	20	76·0	19–123	19	27·3
B	10–122	20	80·0	20– 79	21	76·9
C	16–117	20	70·0	20– 66	22	63·6
ALL GROUPS	10–122	—	75·3	19–123	—	55·9

Group.	Third Period, 1932–1933.			Fourth Period, 1933–1934.		
	Dioestrous Periods.		Percentage of Cases in which Oestrus Recurred after the Normal Interval of 18–23 Days.	Dioestrous Periods.		Percentage of Cases in which Oestrus Recurred after the Normal Interval of 18–23 Days.
	Range.	Mode.		Range.	Mode.	
	Days.	Days.		Days.	Days.	
A	19–112	22	57·1	20–44	21	30·8
B	19– 80	21	50·0	19–44	19, 20, 21, 22 and 24	36·8
C	20– 77	—	33·3	20–82	20, 22, 23, 41	50·0
ALL GROUPS	19–112	—	46·8	19–82	—	39·2

TABLE XII.

Gestation Periods: Frequencies.

(*a*) *First Calving.*

Groups.	Gestation Periods in Days.																					Totals.
	264	269	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	
A	—	—	—	—	—	—	1	—	2	—	—	2	2	—	—	—	1	—	—	—	—	8
B	—	—	—	—	—	—	—	—	1	1	1	—	1	—	—	—	—	—	2	—	—	6
C	—	—	1	—	—	—	—	—	1	—	1	—	—	2	—	—	—	1	—	1	1	8

(*b*) *Second Calving.*

Groups.	264	269	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	Totals.
A	—	—	—	1	—	—	—	—	1	—	1	—	1	1	—	2	—	1	—	—	—	8
B	1	—	—	—	—	—	—	—	—	—	1	—	2	2	—	1	1	1	—	—	—	9
C	—	—	—	—	—	1	—	—	1	—	—	1	2	1	—	2	—	1	—	—	—	9

(*c*) *Third Calving.*

Groups.	264	269	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	Totals.
A	—	—	—	—	—	—	1	1	—	1	—	—	2	1	1	—	1	—	—	—	—	8
B	—	—	—	—	—	—	—	2	—	—	1	2	2	1	—	—	—	1	—	—	—	9
C	—	—	—	—	—	1	—	1	1	—	2	—	—	—	—	2	—	2	—	—	—	9

(*d*) *Fourth Calving.*

Groups.	264	269	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	Totals.
A	—	—	—	1	1	—	—	—	—	1	1	—	—	1	1	—	1	—	—	—	—	7
B	—	—	—	1	1	—	—	3	1	—	—	—	—	1	—	—	—	—	—	—	—	7
C	—	2	—	1	—	—	—	1	—	2	—	1	—	—	—	—	—	—	—	—	—	7
A (four calvings)	—	—	—	2	1	—	2	1	3	2	2	2	5	3	2	2	3	1	—	—	—	31
B "	1	—	—	1	1	—	—	5	2	1	3	2	5	4	—	1	1	2	2	—	—	31
C "	—	2	1	1	—	2	—	2	3	2	3	2	2	3	—	4	—	4	—	1	1	33
TOTALS	1	2	1	4	2	2	2	8	8	5	8	6	12	10	2	7	4	7	2	1	1	95

TABLE XIII.

Gestation Periods.

Group.	Sex.	First Period.			Second Period.			Third Period.			Fourth Period.			All Periods.		
		No.	Gestation Period.		No.	Gestation Period.		No.	Gestation Period.		No.	Gestation Period.		No.	Gestation Period.	
			Range.	Average.		Range.	Average.		Range.	Average.		Range.	Average.		Range	Average.
			Days.	Days.		Days.	Days.		Days.	Days.		Days.	Days.		Days.	Days.
A.........	M.	4	275–285	279·2	4	277–282	279·7	4	278–285	281 7	3	273–279	276·7	15	273–285	279·3
	F.	4	277–281	279 7	4	272–286	281·5	3	275–282	279 3	5	272–282	279·6	16	272–286	280 0
B.........	M.	2	279–287	283·0	2	281–282	281·5	5	276–286	280 6	5	273–282	276·8	13	273–287	280·5
	F.	4	277–287	280·8	7	264–285	280·1	4	276–282	279 5	2	272–279	275 5	17	264–287	279·0
C.........	M.	5	271–288	279·4	4	280–286	282·8	4	276–286	280·7	3	272–280	276·0	16	271–288	279·7
	F.	3	282–289	285·7	5	274–284	279·6	5	274–286	280·4	4	269–278	273·5	17	269–289	279·8
ALL GROUPS..	M.	11	271–288	280·0	10	277–286	281·3	13	276–286	281 0	11	272–282	276·5	45	271–288	279·7
	F.	11	277–289	281·7	16	264–286	280·3	12	274–286	279·7	11	269–282	276·2	50	264–289	279·5

M. = Males. F. = Females.

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